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# Systematic Reviews

## Patient characteristics as effect modifiers for psoriasis biologic treatment response: an assessment using network meta-analysis subgroups

--Manuscript Draft--

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| <b>Manuscript Number:</b>                            | SYSR-D-20-00009R2  |
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| <b>Article Type:</b>                                 | Research   |
| <b>Funding Information:</b>                          |  |
| <b>Abstract:</b>                                     | <p>Abstract</p> <p>Background: Network meta-analyses (NMAs) of psoriasis treatments, undertaken as part of the NICE Single Technology Appraisal (STA) process, have included heterogeneous studies. When there is inconsistency or heterogeneity across the different comparisons or trials within the network of studies, the results of the NMA may not be valid. We explored the impact of including studies with heterogeneous patient characteristics on the results of NMAs of psoriasis treatments.</p> <p>Methods: All NMAs undertaken for psoriasis STAs were identified and the included studies tabulated, including patient characteristics that may influence relative treatment effects. In addition to the original network of all studies using licensed treatment doses, a range of smaller, less heterogeneous networks were mapped: 'no previous biologic use' (&lt;25% patients had prior biologic therapy exposure), 'Psoriasis Area and Severity Index score ≤25', 'weight ≤90 kg' and 'white ethnicity' (≥90% patients were white).</p> <p>Results: Sixty-nine studies were included in our synthesis (34,924 participants). A random effects model with a log-normal prior distribution was chosen for each of the subgroup NMAs. Heterogeneity was reduced for the four smaller networks.</p> <p>There were no significant differences in the relative treatment effect (PASI 75 response) for each treatment across the five NMAs, with all credible intervals overlapping, although there were noticeable differences. Treatment rankings based on the median relative risks were also generally consistent across the networks. However, the NMA that included only studies in which &lt;25% patients had prior biologic therapy exposure had slightly different treatment rankings; the anti-TNF therapies certolizumab pegol and infliximab ranked higher in this network than any other network, although credible intervals were large.</p> <p>Conclusions: This work has highlighted potential differences in treatment response for biologic-naïve patients. When conducting NMAs in any area, heterogeneity in patient characteristics of included trials should be carefully assessed and effect modification related to certain patient characteristics investigated through clinically relevant subgroup analyses.</p> |
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| <b>Response to Reviewers:</b>                  | <p>Reviewer 1: I'd like to thank the authors for considering my comments and making relevant revisions. My concerns have been addressed.</p> <p>Authors' response: No response required.</p> <p>Reviewer 3: This work uses a method that highlight potential differences effectiveness patients receiving psoriasis treatment.</p> <p>In addition, emphasizes importance of assessing heterogeneity in patient characteristics, and adjusting for effect modifiers in a NMA, restricting inclusion in the NMA to certain subgroups of patients with similar characteristics.</p> <p>Obviously, focusing the inclusion criteria to produce smaller, more homogenous networks can reduce the risk of both heterogeneity and inconsistency, and give more reliable results.</p> <p>Therefore, the results support the assumption that prior exposure to biologic therapy is associated with psoriasis treatment response and confirm the importance of considering this as a potential effect modifier.</p> <p>However, it seems surprising to say that future decision-making on psoriasis treatments should consider "this subgroup" when undertaking network meta-analysis.</p> <p>The "Conclusions" could be discussed differently.</p> <p>Authors' response: The wording of the sentence about future decision-making has been amended in the conclusions section, as follows: Future decision-making on psoriasis treatments should consider patients' prior exposure to biologic therapies.</p> <p>We have also amended the discussion section, adding a sentence to the paragraph about further investigation of our findings using IPD, as follows: Where individual patient data are available, a better characterisation of patients' prior biologic use could be used to further explore the differences identified.</p> |
| <b>Additional Information:</b>                 |   |
| <b>Question</b>                                | <b>Response</b>   |
| Covering letter concerning your manuscript     | <p>Dear Sir/Madam</p> <p>On behalf of myself and my colleagues, I wish to submit this manuscript to Systematic Reviews for consideration for publication.</p> <p>The manuscript describes a methodological research project in which we explored the impact of heterogeneous patient characteristics on the results of network meta-analyses of psoriasis treatments undertaken as part of the NICE Single Technology Appraisal process. This work highlights potential differences in relative treatment effectiveness for biologic-naïve patients receiving psoriasis treatment, which may have implications for clinical practice. The work demonstrates the importance of assessing heterogeneity and adjusting for effect modifiers in a network meta-analysis, which can be done by restricting inclusion criteria to subgroups of patients with similar characteristics. We believe that this paper will be of interest to readers involved in undertaking network meta-analyses.</p> <p>All authors have approved the manuscript, the content of which has not be submitted</p>   |

for publication elsewhere.

Thank you for your consideration.

Yours faithfully

Ros Wade  
Research Fellow  
Centre for Reviews and Dissemination

# Research article

## Patient characteristics as effect modifiers for psoriasis biologic treatment response: an assessment using network meta-analysis subgroups

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### Abstract

Background: Network meta-analyses (NMAs) of psoriasis treatments, undertaken as part of the NICE Single Technology Appraisal (STA) process, have included heterogeneous studies. When there is inconsistency or heterogeneity across the different comparisons or trials within the network of studies, the results of the NMA may not be valid. We explored the impact of including studies with heterogeneous patient characteristics on the results of NMAs of psoriasis treatments.

Methods: All NMAs undertaken for psoriasis STAs were identified and the included studies tabulated, including patient characteristics that may influence relative treatment effects. In addition to the original network of all studies using licensed treatment doses, a range of smaller, less heterogeneous networks were mapped: ‘no previous biologic use’ (<25% patients had prior biologic therapy exposure), ‘Psoriasis Area and Severity Index score  $\leq 25$ ’, ‘weight  $\leq 90$  kg’ and ‘white ethnicity’ ( $\geq 90\%$  patients were white).

Results: Sixty-nine studies were included in our synthesis (34,924 participants). A random effects model with a log-normal prior distribution was chosen for each of the subgroup NMAs. Heterogeneity was reduced for the four smaller networks.

There were no significant differences in the relative treatment effect (PASI 75 response) for each treatment across the five NMAs, with all credible intervals overlapping, although there were noticeable differences. Treatment rankings based on the median relative risks were also generally consistent across the networks. However, the NMA that included only studies in which <25% patients had prior biologic therapy exposure had slightly different treatment rankings; the anti-TNF therapies certolizumab pegol and infliximab ranked higher in this network than any other network, although credible intervals were large.

Conclusions: This work has highlighted potential differences in treatment response for biologic-naïve patients. When conducting NMAs in any area, heterogeneity in patient characteristics of included trials should be carefully assessed and effect modification related to certain patient characteristics investigated through clinically relevant subgroup analyses.

## Key words

Heterogeneity, Indirect comparison, Network meta-analysis, Single Technology Appraisal, Psoriasis

## Background

Network meta-analysis (NMA) has become increasingly popular over recent years for estimating the relative effectiveness of several treatments in the absence of direct head-to-head evidence. When direct and indirect evidence is combined in a meta-analysis, there is a risk that patients in different trials differ in terms of demographics, disease or other patient characteristics. There can also be differences in trial specific features, such as country of origin and trial design. If these differences are effect modifiers, they can result in between-

1 study heterogeneity and create biased comparisons. In a NMA context, such biases and  
2 heterogeneity can also lead to inconsistency, i.e. conflict between direct and indirect evidence  
3 on the same comparison. It is therefore important to adjust for effect modifiers in a NMA;  
4 this can be done by restricting inclusion in the NMA to certain subgroups of patients with  
5 similar characteristics or by conducting meta-regression. Focusing the inclusion criteria on  
6 key participant or study characteristics to produce smaller, more homogenous networks can  
7 reduce the risk of both heterogeneity and inconsistency, and give more valid results.(1)  
8 Alternatively, meta-regression, on for example the average weight or proportion of included  
9 patients with certain characteristics, can also be conducted. When conducting network meta-  
10 regression, a sufficient number of studies is needed to estimate independent coefficients for  
11 each treatment comparison. Otherwise, additional assumptions of common regression  
12 coefficients must be made, which may not be clinically plausible. In addition, results are  
13 often uncertain and hard to interpret. Therefore it is often more useful to identify clinically  
14 meaningful discrete participant and study characteristics which could be expected to lead to  
15 different decisions, and restrict inclusion in the NMA.

16 Previous work carried out for the National Institute for Health and Care Excellence (NICE)  
17 has highlighted that several NMAs undertaken for NICE Single Technology Appraisals  
18 (STAs) of psoriasis treatments have included heterogeneous studies. However, the very short  
19 timeframe of a STA does not allow sufficient time to fully explore the impact of  
20 heterogeneity on the NMA results.(2) Therefore, this small methodological project aimed to  
21 explore the impact of heterogeneous patient characteristics on the results of a NMA, using  
22 data from NICE STAs of psoriasis treatments, since we identified this as an area where  
23 previous NMAs have included studies with heterogeneous patient characteristics.

1 There have been several NICE STAs of systemic therapies for the second-line treatment of  
2 moderate-to-severe plaque psoriasis. Psoriasis is a chronic, inflammatory immune-mediated  
3 skin disorder with a prevalence of around 3% in the UK.(3) Standard first-line treatment  
4 includes topical therapy, or systemic non-biologic therapies or phototherapy for patients with  
5 more severe disease. For adults with moderate-to-severe psoriasis who do not respond to, are  
6 intolerant of, or have a contraindication to standard systemic therapies and phototherapy,  
7 NICE recommends systemic biologic therapies, apremilast or dimethyl fumarate.

8 The severity of psoriasis is measured using the Psoriasis Area and Severity Index (PASI),  
9 which combines the assessment of severity of lesions and the area affected into a single score.  
10 PASI is also used to assess response to psoriasis treatment, presented as a percentage  
11 response rate; PASI 75 response is a 75% or greater improvement in PASI score, PASI 90  
12 response is a 90% or greater improvement and PASI 100 response is 100% improvement in  
13 PASI score (total skin clearance).

14 The key objectives of this methodological project were:

- 15 (i) To identify NMAs undertaken as part of a STA of a second-line therapy for  
16 moderate to severe plaque psoriasis;
- 17 (ii) To identify and tabulate all relevant studies included in the NMAs, recording  
18 patient and study characteristics that may influence relative treatment effects  
19 (PASI response);
- 20 (iii) To map a range of smaller, less heterogeneous networks; and
- 21 (iv) To run the NMAs and compare results with the results of the overall network  
22 of evidence.



## 1   **Methods**

2   Two researchers (RW and SS) independently screened the NICE website for STAs of second-  
3  
4   line therapies for moderate to severe plaque psoriasis that included a NMA. The researchers  
5  
6  
7   4   also identified any sensitivity analyses undertaken by the company who undertook the NMA,  
8  
9  
10   5   as an indication of the characteristics that may be considered to have an impact on relative  
11  
12   6   treatment effectiveness.

13  
14  
15   7   All studies included in the NMAs were tabulated. Additional RCTs of second-line therapies  
16  
17  
18   8   for psoriasis were not sought since the search strategies used in the STAs were adequate and  
19  
20   9   the aim of this methodological project was to compare results of NMA subgroups with the  
21  
22   10   original network, rather than to update the previous NMAs. Details of important patient and  
23  
24  
25   11   study characteristics that may influence relative treatment effects were tabulated, such as  
26  
27  
28   12   timeframe at which treatment response was assessed, drug dose, concomitant psoriatic  
29  
30   13   arthritis and prior treatments received (i.e. biologic naïve versus biologic experienced  
31  
32   14   patients). Dermatologists who had acted as clinical advisors to the Centre for Reviews and  
33  
34  
35   15   Dissemination/Centre for Health Economics Technology Assessment Group in previous  
36  
37  
38   16   STAs of second-line therapies for psoriasis were emailed regarding their opinion on the  
39  
40   17   characteristics considered most likely to have an impact on the relative effectiveness of  
41  
42   18   psoriasis treatments on PASI response. The outcome used in the analysis was PASI 75  
43  
44  
45   19   response, as it is the most widely reported response outcome in the included trials and is used  
46  
47   20   as a measure of treatment response in clinical practice.

48  
49  
50  
51   21   Study details were obtained from tables presented as part of the STA of brodalumab,(4)  
52  
53   22   supplemented with data presented in primary study reports, where necessary. The  
54  
55   23   brodalumab appraisal was chosen as the primary source of data because it included  
56  
57  
58   24   comprehensive study characteristics tables. The tables were independently checked for

1 accuracy and completeness by a second researcher using tables from two different STAs,  
2 supplemented with data presented in primary study reports. All missing data/discrepancies  
3 were added/corrected using the original study reports.

4 Study and patient characteristics considered most likely to have an impact on relative  
5 treatment effectiveness were compared for each of the primary studies. New networks,  
6 including only studies with similar study and patient characteristics, were defined and  
7 mapped using the netmeta package(5) in R.(6) This package uses contrast-level data to create  
8 plots of all the trials included in the NMA, highlighting the number of trials between each  
9 treatment. All networks were checked for connectivity, making sure that all interventions  
10 were directly connected to at least one other intervention, forming one linked network.

11 Binomial logit-link models were used for the NMAs.(2) Both fixed effect and random effects  
12 models were fitted for each network. The choice of prior distributions for the between-study  
13 variance was also explored. Model fit was assessed by comparing the total residual deviance  
14 to the number of data points in the model. Models were compared using the deviance  
15 information criterion (DIC) which accounts for model fit and complexity. The model with a  
16 lower DIC (a difference in value of 3 is seen as meaningful) was selected. Where the DIC  
17 were within 3 points of each other, the simplest model with fewer parameters was chosen.

## 18 **Results**

### 19 ***Review of NICE Technology Appraisals***

20 There have been ten NICE STAs of systemic therapies for the second-line treatment of  
21 moderate-to-severe plaque psoriasis. The second-line systemic therapies that have been  
22 appraised are the anti-tumour necrosis factor (TNF) alpha therapies adalimumab, infliximab  
23 and certolizumab pegol, the anti-interleukin (IL)-12/23 ustekinumab, the anti-IL-17 therapies  
24 secukinumab, ixekizumab and brodalumab, the anti-IL-23 tildrakizumab, the anti-

phosphodiesterase (PDE) 4 apremilast and the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activator dimethyl fumarate. Other than infliximab, which is only recommended for patients with very severe disease, each of the company submissions included a NMA (see Table 1).

**Table 1: NICE Single Technology Appraisals of systemic therapies for psoriasis that include network meta-analyses**

| Psoriasis systemic therapy          | Treatment class | Number of trials included in NMA       | Sensitivity analyses undertaken  |
|-------------------------------------|-----------------|--|--|
| Adalimumab (TA146, 2008)(7)         | Anti-TNF-alpha  | 18 randomised controlled trials (RCTs) | N/A  |
| Ustekinumab (TA180, 2009)(8)        | Anti-IL-12/23   | 20 RCTs                                | N/A  |
| Secukinumab (TA350, 2015)(9)        | Anti-IL-17      | 26 RCTs                                | Baseline PASI score; psoriasis duration; prior biologic therapy exposure; baseline Dermatology Life Quality Index (DLQI) score |
| Apremilast (TA419, 2016)(10)        | Anti-PDE4       | 22 RCTs                                | Prior biologic therapy exposure  |
| Ixekizumab (TA442, 2017)(11)        | Anti-IL-17      | 40 RCTs                                | All treatment doses (base case included only NICE-approved doses)  |
| Dimethyl fumarate (TA475, 2017)(12) | Nrf2 activator  | 37 RCTs                                | N/A  |

|   |   |                |         |  |
|---|---|----------------|---------|--|
| 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9 | Brodalumab<br>(TA511, 2018)(4)          | Anti-IL-17     | 59 RCTs | NICE-approved treatment doses; timing of<br>primary outcome assessment; trial size; prior<br>biologic therapy exposure; baseline PASI<br>score |
| 10<br>11<br>12<br>13<br>14                | Certolizumab pegol<br>(TA574, 2019)(13) | Anti-TNF-alpha | 65 RCTs | Prior biologic therapy exposure  |
| 15<br>16<br>17<br>18<br>19<br>20          | Tildrakizumab<br>(TA575, 2019)(14)      | Anti-IL-23     | 45 RCTs | Timing of primary outcome assessment   |

## 2 ***Patient characteristics that may contribute to heterogeneity in relative treatment effects***

3 Sensitivity analyses undertaken alongside the STA NMAs related to the following  
4 study/patient characteristics: size of the trial; licensed and NICE approved treatment doses;  
5 timing of primary outcome assessment; patients' baseline PASI score; patients' baseline  
6 DLQI score; duration of disease; and prior exposure to biologic therapy. Two dermatologists  
7 (Professor Catherine Smith and Dr Phil Hampton) provided advice on the study and patient  
8 characteristics considered most likely to have an impact on the relative effectiveness of  
9 psoriasis treatments on PASI response. Important characteristics for which adequate data  
10 were available in the studies of psoriasis treatments were patient weight, exposure to previous  
11 biologic therapy, white versus non-white ethnicity and baseline PASI score.

## 12 ***Network identification***

13 We identified 72 studies from previous NMAs of STAs of second-line therapies for moderate  
14 to severe plaque psoriasis. We excluded any studies with unlicensed treatments or treatment  
15 doses, of which there were two. One study was excluded due to the results being unpublished.

Therefore, we included 69 studies in our synthesis (34,924 participants). Characteristics of patients included in the 69 RCTs included in the networks are presented in Additional file 1.

The impact of four patient characteristics on relative treatment effectiveness was investigated by producing four smaller networks: ‘no previous biologic use’ (<25% patients had prior exposure to a biologic therapy), ‘PASI  $\leq 25$ ’ (average PASI score was 25 or less), ‘weight  $\leq 90$  kg’ (average weight was 90 kg or less) and ‘white ethnicity’ ( $\geq 90\%$  patients were white). Cut-off choice was informed by clinical opinion as well as being pragmatically chosen in order to ensure a sufficient number of studies was still included in each network. The studies included in each of the four networks and the original (all licensed doses) network are listed in Table 2. The network diagrams are shown in Figures 1 to 5. The width of the connecting lines is proportional to the number of trial level comparisons available and the size of the nodes is proportional to the number of patients who received the corresponding treatment.

*Insert Table 2 here*

### ***Model fit***

In all models both a uniform (0,3) prior distribution and an empirically based log normal (-2.70,1.52<sup>2</sup>) informative prior distribution(15) were used. The random effects model with a uniform prior distribution was found to have a superior fit for the network of all studies with licensed doses (Table 3) as the residual deviance was closer to the number of unconstrained data points than the fixed effects model and the random effects model with log-normal prior distribution. The deviance information criterion (DIC) was also lower for the uniform prior random effects model than the other two models.

*Insert Table 3 here*

The random effects model with a log-normal prior distribution was chosen for the network of patients with no previous biologic use (<25% patients had previous biologic use), the network of patients with PASI score  $\leq 25$ , the network of patients with weight  $\leq 90$  kg and the network of  $\geq 90\%$  white patients (Table 3). The DIC and residual deviance was much lower for the random effects models than the fixed effects models. Although the DIC was very similar between the random effects models, the log-normal prior model was chosen as it had a much smaller number of parameters (pD) than the uniform prior model.

### ***Heterogeneity***

The network of all studies with licensed doses had the highest between-study heterogeneity (0.31, 95% CrI: 0.17-0.45). The between-study heterogeneity was reduced for the four smaller networks, which all had similar values. However, the network of patients with no previous biologic use had the smallest heterogeneity (0.14, 95% CrI: 0.09-0.23), alongside the network of patients with weight  $\leq 90$  kg (0.15, 95% CrI: 0.09-0.24). The densities of the posterior between-study heterogeneity for each network meta-analysis are shown in Figure 6.

### ***Effects of the interventions***

Relative risk ratios for each treatment compared against placebo are shown in Table 4. Across the five NMAs, the relative risks for each treatment appear to be similar, with all credible intervals overlapping. However, there are some noticeable differences. Etanercept 50 mg (once-weekly) had a higher relative treatment effect of achieving PASI 75 in the licensed doses network (10.67, 95% CrI: 7.96-13.53) compared to all other networks and methotrexate had a higher relative effect in the network of patients with no previous biologic use (<25% had previous use) (10.47, 95% CrI: 6.73-14.41) compared to the other networks. In the  $\geq 90\%$  white patients network, secukinumab had a higher relative treatment effect than in all other networks (18.67, 95% CrI: 16.22-20.81) and guselkumab had a lower relative treatment effect

1 compared to all the other networks (15.30, 95% CrI: 10.89-18.39). However, their credible  
2 intervals were large.

3 *Insert table 4 here*

4 Log-odds ratios for each network and for each treatment compared to placebo are shown in  
5 Figure 7. Absolute probabilities of achieving PASI 75 for each treatment across the five  
6 networks are shown in Additional file 2.

7 The median rankings of treatments based on the relative risks are shown in Table 5.

8 Ixekizumab ranks best in all networks, except the network with predominantly white patients,  
9 in which secukinumab ranks best. Dimethyl fumarate ranks worst in all five networks. The  
10 rankings are generally consistent across the networks. However, the NMA that included only  
11 studies in which less than 25% of patients had prior exposure to a biologic therapy had  
12 slightly different treatment rankings; the anti-TNF therapies certolizumab pegol (median rank  
13 of 8 [95% CrI: 2-13] for the 200mg dose and 6 [95% CrI: 1-11] for the 400 mg dose) and  
14 infliximab (median rank of 3 [95% CrI: 3-11]) ranked higher in this network group than any  
15 of the other networks, indicating that these two therapies may work better in patients who  
16 have not previously received biologic therapy, although we note the large uncertainty in these  
17 rankings. However, biologic experienced patients are more likely to have had prior exposure  
18 to an anti-TNF therapy (i.e. adalimumab or etanercept) which may explain why subsequent  
19 response to the anti-TNF therapies certolizumab pegol and infliximab was lower in the  
20 networks that did not include primarily biologic-naïve patients.

21 *Insert table 5 here*

22 The network of primarily white patients also had slightly different treatment rankings;  
23 secukinumab ranked higher and guselkumab ranked lower than in the other networks,

1 although there was large uncertainty for the guselkumab result. Data on ethnicity was often  
2 not reported in the included studies, so some assumptions had to be made based on the  
3 location of the study when extracting data from primary studies, adding further uncertainty to  
4 the results for this network.

### 5 *Sensitivity analysis*

6 Some studies of the earlier treatments for psoriasis, adalimumab, etanercept and infliximab,  
7 did not report prior biologic use, however they may have had largely biologic-naïve patient  
8 populations as biologics were not widely available at the time they were conducted.  
9 Therefore, all the studies not already included in the network of patients who had no prior  
10 biologic exposure (<25% patients) were screened and studies conducted prior to 2007, where  
11 prior biologic use was not reported, were added to the network. The cut-off of 2007 was  
12 chosen to ensure that all the earliest studies were included. Six studies conducted prior to  
13 2007 were identified and included in the network: Gottlieb et al. (2003),(16) Leonardi et al.  
14 (2003),(17) Papp et al. (2005),(18) Reich et al. (2005),(19) Gordon et al (2006)(20) and  
15 Tying et al. (2006).(21) The random effects model with a log-normal prior distribution was  
16 chosen for the network of patients with no previous biologic use (<25% patients had previous  
17 biologic use) (see Additional file 3, Table 1).

18 The results from the sensitivity analysis were very similar to the main results (see Additional  
19 file 3, Table 2). There were minimal changes to the risk ratios, with very little difference in  
20 the anti-TNF drugs adalimumab, infliximab and etanercept. There were a few small changes  
21 to other treatments. The median ranking of guselkumab changed from 3 to 4, with the same  
22 credible interval of 1-7. The median ranking of apremilast and DMF dropped one rank each,  
23 with the addition of etanercept 25 mg to the network, making the total number of treatments  
24 17, rather than 16.



## Discussion

The smaller networks investigated were less heterogeneous, with between-study standard deviation ranging from 0.14 (95% CrI: 0.09-0.23) for the network of patients with no previous biologic use to 0.17 (95% CrI: 0.10-0.25) for the network of predominantly white patients, in comparison with the network of all studies with licensed doses (0.31, 95% CrI: 0.17-0.45). The reduction in heterogeneity in the network of patients with no previous biologic use could be due to the population being more clinically homogenous. Previous biologic use may be an important effect modifier and so excluding patients with previous biologic use may have removed a significant source of heterogeneity.

Results for most of the NMAs were consistent, in terms of treatment rankings for PASI 75 response. The main exception was the NMA of studies in which  $\leq 25\%$  patients had prior exposure to a biologic therapy; in this network results were better for the anti-TNF therapies certolizumab pegol and infliximab than in the other networks. Whilst this could simply reflect the fact that studies in which a higher proportion of patients had prior exposure to a biologic therapy had used an anti-TNF as the prior therapy (i.e. adalimumab or etanercept), this may be an important effect modifier. Prior biologic therapy exposure was the most commonly conducted sensitivity analysis amongst the NICE STAs of systemic therapies for psoriasis that included a NMA (see Table 1) and our results confirm the importance of considering this as a potential effect modifier.

Meta-regression is another method commonly used to adjust for effect modifiers. However, this requires a sufficient number of studies in order to estimate independent coefficients for each treatment comparison. Additional file 4 presents the number of studies that reported each continuous covariate for each treatment comparison. This shows that there are not enough studies between comparisons to estimate independent coefficients and a common

1 regression coefficient would need to be assumed, which may not be clinically credible.  
2 Therefore, analyses were simplified by dichotomising variables according to clinically  
3 relevant cut-offs and creating separate networks. Previous work has investigated the effect of  
4 baseline risk using meta-regression.(22) Baseline risk is often a proxy for multiple observed  
5 and unobserved effect modifiers and does not describe specific individual patient-related  
6 treatment effect modifiers. Adjusting for baseline risk in this analysis may not be clinically  
7 meaningful for decision making since it is uncertain what determines the baseline risk. Our  
8 aim was to characterise heterogeneity based on known and previously hypothesised study-  
9 level characteristics that translate to individual patient characteristics, which can be used to  
10 focus decision-making on more specific, homogeneous populations.

11 A limitation of our analysis is the variation in time point at which PASI 75 was assessed in  
12 the included studies. In most included studies the time point for the primary efficacy  
13 assessment was week 12, although in some studies it was week 16; adalimumab, apremilast,  
14 certolizumab pegol, tildrakizumab and ustekinumab were assessed at week 12 in some  
15 studies and week 16 in others. The primary efficacy assessment was week 10 in placebo-  
16 controlled trials of infliximab, reflecting the shorter time to treatment effect for this therapy.

17 Our findings could be investigated further using individual patient data meta-analysis  
18 accounting for different important covariates. However, this preliminary approach has  
19 highlighted potential differences in treatment response for patients with prior exposure to  
20 biologic therapy. Where individual patient data are available, a better characterisation of  
21 patients' prior biologic use could be used to further explore the differences identified.

## 22 ***Comparison with other results***

23 Treatment rankings for the 'licenced doses' NMA were broadly consistent with the results of  
24 the NMA undertaken by the guideline development group for the BAD guidelines for

biologic therapy for psoriasis, published in April 2017.(23) The BAD NMA compared ixekizumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. Interventions were ranked in order of efficacy using the surface under the cumulative ranking (SUCRA) curve method. For the outcome PASI 75 at 3-4 months ixekizumab ranked best (SUCRA 96.4, mean rank 1.3), followed by infliximab (SUCRA 81.2, mean rank 2.3), secukinumab (SUCRA 79.0, mean rank 2.5), ustekinumab (SUCRA 51.9, mean rank 4.4), adalimumab (SUCRA 48.7, mean rank 4.6), etanercept (SUCRA 28.4, mean rank 6.0), methotrexate (SUCRA 14.5, mean rank 7.0) and placebo (SUCRA 0, mean rank 8.0). However, the BAD NMA pooled licensed and unlicensed doses.(24) It included many unlicensed doses that were not included in this analysis as they are not relevant for decision-making. Naïve pooling across doses, without accounting for possible differential dose effects, is not recommended as it can increase heterogeneity due to different treatment definitions. Furthermore, the aim of this analysis was to characterise heterogeneity in networks used by NICE, therefore only licenced doses were relevant.

A recent article evaluated the association between patient characteristics and response to biologic therapies for psoriasis, using a multicentre longitudinal cohort study; the British Association of Dermatologists Biologic Interventions Register (BADBIR).(25) This study also found little evidence for predictors of differential treatment response, although only biologic-naïve patients were included in the study.

## ***Network structure***

There was some overlap between networks in terms of included studies (see Table 2). In particular many of the studies excluded from the  $\geq 90\%$  white patients network were included in the network of studies with lighter patients ( $\leq 90$  kg). Only ten studies included patients

with a mean weight below 80 kg, nine of which were conducted in Japanese, Chinese or mixed Taiwanese, Chinese and Korean patients (See Additional file 1).

### ***Recommendations for future research***

NMAs of psoriasis treatments undertaken in the future should investigate heterogeneity within the networks and include clinically relevant subgroups to further investigate effect modification related to certain patient characteristics. This recommendation is also appropriate for NMAs in other clinical areas and other fields outside of medicine.

### **Conclusions**

This work has highlighted potential differences in relative treatment effectiveness for biologic-naïve patients receiving psoriasis treatment. Our results support the assumption that prior exposure to biologic therapy is associated with psoriasis treatment response and confirm the importance of considering this as a potential effect modifier. Future decision-making on psoriasis treatments should consider patients' prior exposure to biologic therapies..

More broadly, we have demonstrated the importance of assessing heterogeneity in patient characteristics and adjusting for effect modifiers in a NMA, which can be done by restricting inclusion in the NMA to certain subgroups of patients with similar characteristics. Focusing the inclusion criteria to produce smaller, more homogenous networks can reduce the risk of both heterogeneity and inconsistency, and give more valid results.

### **List of abbreviations**

|        |   |
|--------|---|
| BADBIR | British Association of Dermatologists Biologic Interventions Register |
| DLQI   | Dermatology Life Quality Index  |
| DIC    | Deviance information criterion  |
| IL     | Interleukin   |
| NICE   | National Institute for Health and Care Excellence                     |

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- 1 NMA Network meta-analysis
- 2 Nrf2 Nuclear factor (erythroid-derived 2)-like 2
- 3 PDE Phosphodiesterase
- 4 PASI Psoriasis Area and Severity Index
- 5 RCT Randomised controlled trial
- 6 STA Single Technology Appraisal
- 7 SUCRA Surface under the cumulative ranking
- 8 TNF Tumour necrosis factor

9 **Declarations**

10 *Ethics approval and consent to participate*

11 Not applicable.

12 *Consent for publication*

13 Not applicable.

14 *Availability of data and materials*

15 All data generated or analysed during this study are included in this published article (and its  
16 supplementary information files).

17 *Competing interests*

18 The authors declare that they have no competing interests.

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20 The authors received no specific funding for this work.

21 *Authors' contributions*

22 RW conceived and designed the project. RW and SS identified the relevant NMAs and  
23 primary studies and tabulated important study and patient characteristics. SS undertook

1 network meta-analyses under the supervision of SD. All authors contributed to drafting the  
2 manuscript and approved the submitted version.

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### 8 *Authors' information*

9 RW has almost 20 years' experience of undertaking systematic reviews. She has completed  
10 three NICE STAs of systemic therapies for the second-line treatment of moderate-to-severe  
11 plaque psoriasis. SS is a systematic reviewer with experience in medical statistics who has  
12 also been involved in a NICE STA of a systemic therapy for psoriasis. SD is a statistician  
13 with interests in Bayesian methods for evidence synthesis and their application to decision  
14 making. She has collaborated with the NICE Decision Support Unit to produce several  
15 technical support documents which provide guidance to those involved in submitting or  
16 critiquing evidence as part of NICE Technology Appraisals and is lead author of a recent  
17 book on network meta-analysis for decision making.

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1 **Table 2: Studies included in each network meta-analysis**

| Studies          | All<br>licensed<br>doses<br>(N=69) | Patients<br>with no<br>previous<br>biologic use<br>( $<25\%$ had<br>previous<br>use)<br>(N=34) | Patients<br>with PASI<br>score $\leq 25$<br>(N=59) | Patients<br>with weight<br>$\leq 90$ kg<br>(N=28) | White<br>patients<br>( $\geq 90\%$<br>white)<br>(N=42) |
|------------------|------------------------------------|--|--|---|--|
| AMAGINE1 2016    | ✓                                  |  | ✓  |   | ✓  |
| AMAGINE2 2015    | ✓                                  |  | ✓  |   | ✓  |
| AMAGINE3 2015    | ✓                                  | ✓  | ✓  | ✓   | ✓  |
| Nakagawa 2016    | ✓                                  | ✓  |  | ✓   |  |
| Papp 2012        | ✓                                  |  | ✓  | ✓   |  |
| CHAMPION 2008    | ✓                                  |  | ✓  | ✓   | ✓  |
| Goldminz 2015    | ✓                                  |  | ✓  |   |  |
| Cai 2016         | ✓                                  | ✓  |  | ✓   |  |
| REVEAL 2008      | ✓                                  | ✓  | ✓  |   | ✓  |
| Asahina 2010     | ✓                                  |  |  | ✓   |  |
| Gordon 2006      | ✓                                  |  | ✓  |   | ✓  |
| XPLORE 2015      | ✓                                  |  | ✓  |   | ✓  |
| Bissonnette 2013 | ✓                                  |  | ✓  |   | ✓  |
| VOYAGE1 2017     | ✓                                  | ✓  | ✓  |   |  |
| VOYAGE2 2017     | ✓                                  | ✓  | ✓  |   |  |
| PSOR005 2012     | ✓                                  |  | ✓  |   | ✓  |
| ESTEEM1 2015     | ✓                                  |  | ✓  |   | ✓  |

|                   |   |   |   |   |   |
|-------------------|---|---|---|---|---|
| ESTEEM2 2015      | ✓ |   | ✓ |   | ✓ |
| Ohtsuki 2017      | ✓ | ✓ | ✓ | ✓ |   |
| LIBERATE 2016     | ✓ | ✓ | ✓ | ✓ | ✓ |
| Leonardi 2003     | ✓ |   | ✓ |   |   |
| Gottlieb 2003     | ✓ |   | ✓ |   | ✓ |
| Papp 2005         | ✓ |   | ✓ |   | ✓ |
| VandeKerkhof 2008 | ✓ |   | ✓ | ✓ | ✓ |
| Bagel 2012        | ✓ | ✓ | ✓ |   |   |
| Bachelez 2015     | ✓ | ✓ | ✓ | ✓ |   |
| Tyring 2006       | ✓ |   | ✓ |   |   |
| PRISTINE 2013     | ✓ | ✓ | ✓ | ✓ |   |
| M10114 2011       | ✓ | ✓ | ✓ |   | ✓ |
| M10315 2011       | ✓ | ✓ | ✓ |   | ✓ |
| reSURFACE2        | ✓ | ✓ | ✓ | ✓ | ✓ |
| PIECE 2016        | ✓ | ✓ | ✓ |   | ✓ |
| Yang 2012         | ✓ |   | ✓ | ✓ |   |
| EXPRESS 2005      | ✓ |   | ✓ | ✓ |   |
| Chaudhari 2001    | ✓ | ✓ | ✓ | ✓ | ✓ |
| SPIRIT 2004       | ✓ |   | ✓ |   | ✓ |
| EXPRESSII 2007    | ✓ | ✓ | ✓ |   | ✓ |
| Torii 2010        | ✓ |   |   | ✓ |   |
| RESTORE1 2011     | ✓ | ✓ | ✓ | ✓ | ✓ |
| UNCOVER1 2016     | ✓ |   | ✓ |   | ✓ |
| UNCOVER2 2015     | ✓ | ✓ | ✓ |   | ✓ |
| UNCOVER3 2015     | ✓ | ✓ | ✓ |   | ✓ |
| IXORAS 2017       | ✓ | ✓ | ✓ | ✓ | ✓ |
| FEATURE 2015      | ✓ |   | ✓ |   | ✓ |

|               |   |   |   |   |   |
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| ERASURE 2014  | ✓ |   | ✓ | ✓ |   |
| FIXTURE 2014  | ✓ | ✓ | ✓ | ✓ |   |
| JUNCTURE 2015 | ✓ | ✓ | ✓ |   | ✓ |
| CLEAR 2015    | ✓ | ✓ | ✓ | ✓ |   |
| PEARL 2011    | ✓ | ✓ | ✓ | ✓ |   |
| PHOENIX1 2008 | ✓ |   | ✓ |   | ✓ |
| PHOENIX2 2008 | ✓ |   | ✓ |   | ✓ |
| LOTUS 2013    | ✓ | ✓ | ✓ | ✓ |   |
| ACCEPT 2010   | ✓ | ✓ | ✓ |   | ✓ |
| Igarashi 2012 | ✓ | ✓ |   | ✓ |   |
| BRIDGE 2017   | ✓ | ✓ | ✓ |   | ✓ |
| Caproni 2009  | ✓ |   | ✓ |   | ✓ |
| Gisondi 2008  | ✓ |   | ✓ |   | ✓ |
| Meffert       | ✓ |   |   |   | ✓ |
| PappD 2015    | ✓ | ✓ |   |   |   |
| ReSURFACE1    | ✓ | ✓ | ✓ | ✓ |   |
| ultIMMA1      | ✓ |   |   |   |   |
| ultIMMA2      | ✓ |   |   |   |   |
| METOP         | ✓ | ✓ | ✓ |   | ✓ |
| Krueger       | ✓ |   | ✓ |   |   |
| Reich 2012    | ✓ | ✓ | ✓ | ✓ | ✓ |
| CIMPACT 2018  | ✓ |   | ✓ | ✓ | ✓ |
| CIMPASI1 2018 | ✓ |   | ✓ |   | ✓ |
| CIMPASI2 2018 | ✓ |   | ✓ |   | ✓ |
| UNVEIL        | ✓ | ✓ | ✓ | ✓ | ✓ |

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**Table 3: Measures of goodness of fit of fixed and random effects models for each of the five network meta-analyses.**

| Measure of goodness of fit  | Random effects<br>(uniform prior) | Random effects<br>(log-normal<br>prior) | Fixed effects |
|---|-----------------------------------|---|---------------|
| <b>Licensed doses network</b>   |                                   |   |               |
| Residual deviance <sup>1</sup>  | 162.78                            | 177.54                                  | 209.77        |
| pD  | 117.98                            | 106.29                                  | 91.61         |
| Deviance information criterion<br>(DIC)   | 280.76                            | 283.83                                  | 301.38        |
| Between-study standard deviation,<br>posterior median (95% credible<br>interval)    | 0.31 (0.17-0.45)                  | 0.19 (0.12-0.28)                        | -             |
| <b>Network of patients with no previous biologic use (&lt;25% had previous use)</b> |                                   |   |               |
| Residual deviance <sup>2</sup>  | 82.10                             | 82.88                                   | 88.85         |
| pD  | 59.12                             | 56.3                                    | 52.45         |
| Deviance information criterion<br>(DIC)   | 141.22                            | 139.20                                  | 141.30        |
| Between-study standard<br>deviation, posterior median (95%<br>credible interval)    | 0.19 (0.01-0.41)                  | 0.14 (0.09-0.23)                        | -             |
| <b>Network of patients with PASI score ≤25</b>                                      |                                   |   |               |
| Residual deviance <sup>3</sup>  | 143.89                            | 152.67                                  | 173.06        |
| pD  | 99.16                             | 90.58                                   | 79.61         |
| Deviance information criterion<br>(DIC)   | 243.05                            | 243.26                                  | 252.67        |

|  |                      |                  |        |
|--|----------------------|------------------|--------|
| Between-study standard deviation, posterior median (95% credible interval) | 0.2574 (0.114-0.408) | 0.16 (0.10-0.24) | -      |
| <b>Network of patients with weight <math>\leq 90</math> kg</b>             |                      |                  |        |
| Residual deviance <sup>4</sup>   | 66.40                | 74.17            | 80.02  |
| pD   | 51.59                | 44.78            | 42.14  |
| Deviance information criterion (DIC)                                       | 117.99               | 118.95           | 122.16 |
| Between-study standard deviation, posterior median (95% credible interval) | 0.40 (0.08-0.76)     | 0.15 (0.09-0.24) | -      |
| <b>Network of <math>\geq 90\%</math> white patients</b>                    |                      |                  |        |
| Residual deviance <sup>5</sup>   | 100.57               | 112.47           | 126.65 |
| pD   | 78.57                | 71.62            | 63.83  |
| Deviance information criterion (DIC)                                       | 179.14               | 184.09           | 190.48 |
| Between-study standard deviation, posterior median (95% credible interval) | 0.311 (0.13-0.51)    | 0.17 (0.10-0.25) | -      |

<sup>1</sup>165 unconstrained data points, pD number of parameters for Licensed doses network <sup>2</sup>80 unconstrained data points, pD

number of parameters <sup>3</sup>143 unconstrained data points, pD number of parameters <sup>4</sup>65 unconstrained data points,

pD number of parameters <sup>5</sup>103 unconstrained data points, pD number of parameters

- 1     ***Table 4: Median risk ratio for each treatment compared against placebo in all five network***
- 2     ***meta-analyses***

| Treatment                          | Median risk ratio versus placebo – PASI 75<br>(95% CrI) |                                    |                        |                        |                        |
|------------------------------------|---|------------------------------------|------------------------|------------------------|------------------------|
|                                    | All licensed<br>doses                                   | No previous<br>biologic use (<25%) | PASI score<br>≤25      | Weight ≤90<br>kg       | ≥90% white<br>patients |
| Adalimumab 40 mg                   | 12.74<br>(11.00-14.49)                                  | 12.48<br>(10.91-14.13)             | 13.09<br>(11.72-14.57) | 12.87<br>(10.29-15.39) | 13.18<br>(11.21-15.15) |
| Brodalumab 210 mg                  | 16.76<br>(15.12-18.53)                                  | 16.45<br>(14.66-18.31)             | 16.62<br>(15.20-18.18) | 16.73<br>(14.97-18.58) | 16.56<br>(15.02-18.24) |
| Certolizumab 200 mg                | 12.07<br>(9.62-14.54)                                   | 13.93<br>(8.63-18.20)              | 12.08<br>(10.30-13.94) | 11.71<br>(9.11-14.27)  | 12.13<br>(10.02-14.26) |
| Certolizumab 400 mg                | 13.47<br>(11.09-15.80)                                  | 15.73<br>(10.81-19.08)             | 13.42<br>(11.65-15.23) | 13.04<br>(10.53-15.46) | 13.48<br>(11.42-15.52) |
| Etanercept 25 mg                   | 7.61<br>(5.52-10.11)                                    | -                                  | 7.64<br>(6.20-9.20)    | -                      | 7.89<br>(5.60-10.51)   |
| Etanercept 50 mg<br>once-weekly    | 10.67<br>(7.96-13.53)                                   | 5.08<br>(3.50-7.07)                | 6.16<br>(4.69-7.90)    | 5.57<br>(3.91-7.65)    | 7.07<br>(4.57-10.20)   |
| Etanercept 50 mg<br>twice per week | 9.90<br>(8.68-11.21)                                    | 9.46<br>(8.27-10.77)               | 10.40<br>(9.47-11.40)  | 9.85<br>(8.27-11.55)   | 10.33<br>(9.01-11.75)  |
| Guselkumab 100 mg                  | 17.06<br>(15.30-18.91)                                  | 16.68<br>(15.07-18.42)             | 16.83<br>(15.32-18.46) | -                      | 15.30<br>(10.89-18.39) |
| Infliximab 5 mg                    | 16.22<br>(14.37-18.15)                                  | 16.88<br>(14.66-19.03)             | 15.46<br>(13.85-17.17) | 14.19<br>(11.76-16.56) | 15.38<br>(13.41-17.36) |
| Ixekizumab 80mg                    | 17.64<br>(16.06-19.36)                                  | 17.42<br>(15.89-19.09)             | 17.79<br>(16.30-19.41) | 17.16<br>(14.67-19.33) | 17.75<br>(16.23-19.41) |
| Risankizumab 150 mg                | 16.46<br>(14.37-18.47)                                  | -                                  | -                      | -                      | -                      |



|                                 |                        |                        |                        |                        |                        |
|---------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Secukinumab 300 mg              | 16.45<br>(14.79-18.23) | 16.03<br>(14.41-17.73) | 16.43<br>(15.03-17.96) | 16.12<br>(14.55-17.82) | 18.67<br>(16.22-20.81) |
| Ustekinumab 45 mg               | 13.59<br>(11.79-15.44) | 12.20<br>(10.32-14.14) | 13.46<br>(12.17-14.84) | 13.04<br>(10.35-15.63) | 13.68<br>(11.95-15.48) |
| Ustekinumab 90 mg               | 14.67<br>(12.85-16.54) | 13.36<br>(11.29-15.38) | 14.51<br>(13.20-15.95) | 14.36<br>(10.18-17.57) | 14.64<br>(13.00-16.37) |
| Ustekinumab (45 mg<br>or 90 mg) | 12.85<br>(11.07-14.67) | 12.96<br>(11.05-14.94) | 13.19<br>(11.79-14.66) | 13.11<br>(10.99-15.20) | 13.14<br>(11.35-14.95) |
| Tildrakizumab 100 mg            | 14.86<br>(12.49-17.02) | 15.03<br>(13.18-16.91) | 15.82<br>(14.25-17.50) | 15.28<br>(13.31-17.21) | 16.21<br>(14.20-18.16) |
| Apremilast                      | 5.80<br>(4.20-7.61)    | 3.77<br>(2.48-5.59)    | 5.17<br>(4.01-6.61)    | 3.91<br>(2.60-5.79)    | 5.46<br>(4.12-7.10)    |
| Dimethyl Fumarate               | 2.97<br>(1.44-5.73)    | 2.97<br>(1.77-4.88)    | 2.97<br>(1.71-5.01)    | -                      | 2.96<br>(1.71-4.98)    |
| Fumaderm                        | 3.31<br>(1.62-6.26)    | 3.32<br>(1.97-5.41)    | 3.31<br>(1.94-5.53)    | -                      | 3.30<br>(1.92-5.48)    |
| Methotrexate                    | 6.15<br>(4.07-8.65)    | 10.47<br>(6.73-14.41)  | 6.50<br>(4.69-8.60)    | 5.49<br>(3.56-8.12)    | 6.30<br>(4.37-8.61)    |
| Acitretin                       | 4.024<br>(1.55-8.39)   | -                      | 4.07<br>(1.59-8.29)    | -                      | 4.29<br>(1.74-8.43)    |
| Cyclosporin 1.5 mg              | 8.10<br>(2.41-16.91)   | -                      | -                      | -                      | 2.14<br>(0.38-10.53)   |
| Cyclosporin 2.5 mg              | 7.10<br>(2.02-16.34)   | -                      | -                      | -                      | 6.76<br>(2.07-16.03)   |

**Table 5: Median rank of treatments according to PASI 75 response in each of the five networks**

| Treatment                           | Median rank (95% CrI)     |   |                           |                          |                                |
|-------------------------------------|---------------------------|---|---------------------------|--------------------------|--------------------------------|
|                                     | Licensed<br>Doses<br>N=69 | No previous<br>biologic use<br>(<25%)<br>N=34 | PASI score<br>≤25<br>N=59 | Weight<br>≤90 kg<br>N=27 | ≥90% white<br>patients<br>N=42 |
| Adalimumab                          | 11 (8-14)                 | 11 (8-12)                                     | 10 (7-12)                 | 9 (5-11)                 | 10 (7-12)                      |
| Apremilast                          | 17 (16-18)                | 15 (14-16)                                    | 16 (15-16)                | 14 (13-14)               | 16 (15-16)                     |
| Brodalumab                          | 3 (1-6)                   | 4 (1-7)                                       | 3 (2-5)                   | 2 (1-4)                  | 4 (2-6)                        |
| Certolizumab 200 mg                 | 13 (9-15)                 | 8 (2-13)                                      | 12 (9-12)                 | 11 (7-12)                | 12 (8-13)                      |
| Certolizumab 400 mg                 | 10 (7-13)                 | 6 (1-11)                                      | 9 (7-11)                  | 8 (5-11)                 | 9 (6-11)                       |
| DMF                                 | 18 (17-18)                | 16 (14-16)                                    | 17 (17-17)                | -                        | 17 (17-17)                     |
| Etanercept 25mg                     | 16 (15-17)                | -   | 14 (14-15)                | -                        | 14 (13-16)                     |
| Etanercept 50mg<br>(twice per week) | 15 (14-15)                | 13 (12-13)                                    | 13 (13-13)                | 12 (11-12)               | 13 (12-14)                     |

|  |            |            |            |            |            |
|--|------------|------------|------------|------------|------------|
| <b>Etanercept 50mg<br/>(once-weekly)</b> | 14 (10-16) | 14 (14-15) | 15 (14-16) | 13 (13-14) | 15 (13-16) |
| <b>Guselkumab</b>                        | 2 (1-6)    | 3 (1-7)    | 2 (2-5)    | -          | 6 (2-12)   |
| <b>Infliximab</b>                        | 5 (2-8)    | 3 (1-7)    | 6 (3-7)    | 6 (3-10)   | 5 (3-9)    |
| <b>Ixekizumab</b>                        | 1 (1-4)    | 1 (1-4)    | 1 (1-1)    | 1 (1-5)    | 2 (1-3)    |
| <b>Risankizumab</b>                      | 4 (1-8)    | -          | -          | -          | -          |
| <b>Secukinumab</b>                       | 4 (2-7)    | 5 (2-7)    | 4 (2-6)    | 3 (1-5)    | 1 (1-3)    |
| <b>Tildrakizumab</b>                     | 7 (4-12)   | 7 (4-9)    | 5 (3-7)    | 4 (2-7)    | 4 (3-7)    |
| <b>Ustekinumab 45 mg</b>                 | 10 (8-13)  | 11 (8-12)  | 9 (8-12)   | 8 (5-11)   | 9 (6-12)   |
| <b>Ustekinumab 45<br/>mg/90 mg</b>       | 11 (8-14)  | 10 (7-12)  | 10 (7-12)  | 8 (5-11)   | 10 (6-12)  |
| <b>Ustekinumab 90 mg</b>                 | 8 (5-10)   | 9 (7-12)   | 7 (6-8)    | 6 (1-11)   | 7 (5-9)    |
| <b>Total number of<br/>treatments</b>    | 18         | 16         | 17         | 14         | 17         |

# Research article

## Patient characteristics as effect modifiers for psoriasis biologic treatment response: an assessment using network meta-analysis subgroups

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### Abstract

Background: Network meta-analyses (NMAs) of psoriasis treatments, undertaken as part of the NICE Single Technology Appraisal (STA) process, have included heterogeneous studies. When there is inconsistency or heterogeneity across the different comparisons or trials within the network of studies, the results of the NMA may not be valid. We explored the impact of including studies with heterogeneous patient characteristics on the results of NMAs of psoriasis treatments.

Methods: All NMAs undertaken for psoriasis STAs were identified and the included studies tabulated, including patient characteristics that may influence relative treatment effects. In addition to the original network of all studies using licensed treatment doses, a range of smaller, less heterogeneous networks were mapped: ‘no previous biologic use’ (<25% patients had prior biologic therapy exposure), ‘Psoriasis Area and Severity Index score  $\leq 25$ ’, ‘weight  $\leq 90$  kg’ and ‘white ethnicity’ ( $\geq 90\%$  patients were white).

Results: Sixty-nine studies were included in our synthesis (34,924 participants). A random effects model with a log-normal prior distribution was chosen for each of the subgroup NMAs. Heterogeneity was reduced for the four smaller networks.

There were no significant differences in the relative treatment effect (PASI 75 response) for each treatment across the five NMAs, with all credible intervals overlapping, although there were noticeable differences. Treatment rankings based on the median relative risks were also generally consistent across the networks. However, the NMA that included only studies in which <25% patients had prior biologic therapy exposure had slightly different treatment rankings; the anti-TNF therapies certolizumab pegol and infliximab ranked higher in this network than any other network, although credible intervals were large.

Conclusions: This work has highlighted potential differences in treatment response for biologic-naïve patients. When conducting NMAs in any area, heterogeneity in patient characteristics of included trials should be carefully assessed and effect modification related to certain patient characteristics investigated through clinically relevant subgroup analyses.

## Key words

Heterogeneity, Indirect comparison, Network meta-analysis, Single Technology Appraisal, Psoriasis

## Background

Network meta-analysis (NMA) has become increasingly popular over recent years for estimating the relative effectiveness of several treatments in the absence of direct head-to-head evidence. When direct and indirect evidence is combined in a meta-analysis, there is a risk that patients in different trials differ in terms of demographics, disease or other patient characteristics. There can also be differences in trial specific features, such as country of origin and trial design. If these differences are effect modifiers, they can result in between-

1 study heterogeneity and create biased comparisons. In a NMA context, such biases and  
2 heterogeneity can also lead to inconsistency, i.e. conflict between direct and indirect evidence  
3 on the same comparison. It is therefore important to adjust for effect modifiers in a NMA;  
4 this can be done by restricting inclusion in the NMA to certain subgroups of patients with  
5 similar characteristics or by conducting meta-regression. Focusing the inclusion criteria on  
6 key participant or study characteristics to produce smaller, more homogenous networks can  
7 reduce the risk of both heterogeneity and inconsistency, and give more valid results.(1)  
8 Alternatively, meta-regression, on for example the average weight or proportion of included  
9 patients with certain characteristics, can also be conducted. When conducting network meta-  
10 regression, a sufficient number of studies is needed to estimate independent coefficients for  
11 each treatment comparison. Otherwise, additional assumptions of common regression  
12 coefficients must be made, which may not be clinically plausible. In addition, results are  
13 often uncertain and hard to interpret. Therefore it is often more useful to identify clinically  
14 meaningful discrete participant and study characteristics which could be expected to lead to  
15 different decisions, and restrict inclusion in the NMA.

16 Previous work carried out for the National Institute for Health and Care Excellence (NICE)  
17 has highlighted that several NMAs undertaken for NICE Single Technology Appraisals  
18 (STAs) of psoriasis treatments have included heterogeneous studies. However, the very short  
19 timeframe of a STA does not allow sufficient time to fully explore the impact of  
20 heterogeneity on the NMA results.(2) Therefore, this small methodological project aimed to  
21 explore the impact of heterogeneous patient characteristics on the results of a NMA, using  
22 data from NICE STAs of psoriasis treatments, since we identified this as an area where  
23 previous NMAs have included studies with heterogeneous patient characteristics.

1 There have been several NICE STAs of systemic therapies for the second-line treatment of  
2 moderate-to-severe plaque psoriasis. Psoriasis is a chronic, inflammatory immune-mediated  
3 skin disorder with a prevalence of around 3% in the UK.(3) Standard first-line treatment  
4 includes topical therapy, or systemic non-biologic therapies or phototherapy for patients with  
5 more severe disease. For adults with moderate-to-severe psoriasis who do not respond to, are  
6 intolerant of, or have a contraindication to standard systemic therapies and phototherapy,  
7 NICE recommends systemic biologic therapies, apremilast or dimethyl fumarate.

8 The severity of psoriasis is measured using the Psoriasis Area and Severity Index (PASI),  
9 which combines the assessment of severity of lesions and the area affected into a single score.  
10 PASI is also used to assess response to psoriasis treatment, presented as a percentage  
11 response rate; PASI 75 response is a 75% or greater improvement in PASI score, PASI 90  
12 response is a 90% or greater improvement and PASI 100 response is 100% improvement in  
13 PASI score (total skin clearance).

14 The key objectives of this methodological project were:

- 15 (i) To identify NMAs undertaken as part of a STA of a second-line therapy for  
16 moderate to severe plaque psoriasis;
- 17 (ii) To identify and tabulate all relevant studies included in the NMAs, recording  
18 patient and study characteristics that may influence relative treatment effects  
19 (PASI response);
- 20 (iii) To map a range of smaller, less heterogeneous networks; and
- 21 (iv) To run the NMAs and compare results with the results of the overall network  
22 of evidence.

## 1   **Methods**

2   Two researchers (RW and SS) independently screened the NICE website for STAs of second-  
3  
4   line therapies for moderate to severe plaque psoriasis that included a NMA. The researchers  
5  
6  
7   4   also identified any sensitivity analyses undertaken by the company who undertook the NMA,  
8  
9  
10   5   as an indication of the characteristics that may be considered to have an impact on relative  
11  
12   6   treatment effectiveness.

13  
14  
15   7   All studies included in the NMAs were tabulated. Additional RCTs of second-line therapies  
16  
17  
18   8   for psoriasis were not sought since the search strategies used in the STAs were adequate and  
19  
20  
21   9   the aim of this methodological project was to compare results of NMA subgroups with the  
22  
23   10   original network, rather than to update the previous NMAs. Details of important patient and  
24  
25   11   study characteristics that may influence relative treatment effects were tabulated, such as  
26  
27  
28   12   timeframe at which treatment response was assessed, drug dose, concomitant psoriatic  
29  
30  
31   13   arthritis and prior treatments received (i.e. biologic naïve versus biologic experienced  
32  
33   14   patients). Dermatologists who had acted as clinical advisors to the Centre for Reviews and  
34  
35   15   Dissemination/Centre for Health Economics Technology Assessment Group in previous  
36  
37  
38   16   STAs of second-line therapies for psoriasis were emailed regarding their opinion on the  
39  
40  
41   17   characteristics considered most likely to have an impact on the relative effectiveness of  
42  
43   18   psoriasis treatments on PASI response. The outcome used in the analysis was PASI 75  
44  
45   19   response, as it is the most widely reported response outcome in the included trials and is used  
46  
47   20   as a measure of treatment response in clinical practice.

48  
49  
50  
51   21   Study details were obtained from tables presented as part of the STA of brodalumab,(4)  
52  
53   22   supplemented with data presented in primary study reports, where necessary. The  
54  
55   23   brodalumab appraisal was chosen as the primary source of data because it included  
56  
57  
58   24   comprehensive study characteristics tables. The tables were independently checked for



1 accuracy and completeness by a second researcher using tables from two different STAs,  
2 supplemented with data presented in primary study reports. All missing data/discrepancies  
3 were added/corrected using the original study reports.

4 Study and patient characteristics considered most likely to have an impact on relative  
5 treatment effectiveness were compared for each of the primary studies. New networks,  
6 including only studies with similar study and patient characteristics, were defined and  
7 mapped using the netmeta package(5) in R.(6) This package uses contrast-level data to create  
8 plots of all the trials included in the NMA, highlighting the number of trials between each  
9 treatment. All networks were checked for connectivity, making sure that all interventions  
10 were directly connected to at least one other intervention, forming one linked network.

11 Binomial logit-link models were used for the NMAs.(2) Both fixed effect and random effects  
12 models were fitted for each network. The choice of prior distributions for the between-study  
13 variance was also explored. Model fit was assessed by comparing the total residual deviance  
14 to the number of data points in the model. Models were compared using the deviance  
15 information criterion (DIC) which accounts for model fit and complexity. The model with a  
16 lower DIC (a difference in value of 3 is seen as meaningful) was selected. Where the DIC  
17 were within 3 points of each other, the simplest model with fewer parameters was chosen.

## 18 **Results**

### 19 ***Review of NICE Technology Appraisals***

20 There have been ten NICE STAs of systemic therapies for the second-line treatment of  
21 moderate-to-severe plaque psoriasis. The second-line systemic therapies that have been  
22 appraised are the anti-tumour necrosis factor (TNF) alpha therapies adalimumab, infliximab  
23 and certolizumab pegol, the anti-interleukin (IL)-12/23 ustekinumab, the anti-IL-17 therapies  
24 secukinumab, ixekizumab and brodalumab, the anti-IL-23 tildrakizumab, the anti-

phosphodiesterase (PDE) 4 apremilast and the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activator dimethyl fumarate. Other than infliximab, which is only recommended for patients with very severe disease, each of the company submissions included a NMA (see Table 1).

**Table 1: NICE Single Technology Appraisals of systemic therapies for psoriasis that include network meta-analyses**

| Psoriasis systemic therapy          | Treatment class | Number of trials included in NMA       | Sensitivity analyses undertaken  |
|-------------------------------------|-----------------|--|--|
| Adalimumab (TA146, 2008)(7)         | Anti-TNF-alpha  | 18 randomised controlled trials (RCTs) | N/A  |
| Ustekinumab (TA180, 2009)(8)        | Anti-IL-12/23   | 20 RCTs                                | N/A  |
| Secukinumab (TA350, 2015)(9)        | Anti-IL-17      | 26 RCTs                                | Baseline PASI score; psoriasis duration; prior biologic therapy exposure; baseline Dermatology Life Quality Index (DLQI) score |
| Apremilast (TA419, 2016)(10)        | Anti-PDE4       | 22 RCTs                                | Prior biologic therapy exposure  |
| Ixekizumab (TA442, 2017)(11)        | Anti-IL-17      | 40 RCTs                                | All treatment doses (base case included only NICE-approved doses)  |
| Dimethyl fumarate (TA475, 2017)(12) | Nrf2 activator  | 37 RCTs                                | N/A  |

|   |   |                |         |  |
|---|---|----------------|---------|--|
| 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9 | Brodalumab<br>(TA511, 2018)(4)          | Anti-IL-17     | 59 RCTs | NICE-approved treatment doses; timing of<br>primary outcome assessment; trial size; prior<br>biologic therapy exposure; baseline PASI<br>score |
| 10<br>11<br>12<br>13<br>14                | Certolizumab pegol<br>(TA574, 2019)(13) | Anti-TNF-alpha | 65 RCTs | Prior biologic therapy exposure  |
| 15<br>16<br>17<br>18<br>19<br>20          | Tildrakizumab<br>(TA575, 2019)(14)      | Anti-IL-23     | 45 RCTs | Timing of primary outcome assessment   |

## 2 ***Patient characteristics that may contribute to heterogeneity in relative treatment effects***

3 Sensitivity analyses undertaken alongside the STA NMAs related to the following  
4 study/patient characteristics: size of the trial; licensed and NICE approved treatment doses;  
5 timing of primary outcome assessment; patients' baseline PASI score; patients' baseline  
6 DLQI score; duration of disease; and prior exposure to biologic therapy. Two dermatologists  
7 (Professor Catherine Smith and Dr Phil Hampton) provided advice on the study and patient  
8 characteristics considered most likely to have an impact on the relative effectiveness of  
9 psoriasis treatments on PASI response. Important characteristics for which adequate data  
10 were available in the studies of psoriasis treatments were patient weight, exposure to previous  
11 biologic therapy, white versus non-white ethnicity and baseline PASI score.

## 12 ***Network identification***

13 We identified 72 studies from previous NMAs of STAs of second-line therapies for moderate  
14 to severe plaque psoriasis. We excluded any studies with unlicensed treatments or treatment  
15 doses, of which there were two. One study was excluded due to the results being unpublished.

Therefore, we included 69 studies in our synthesis (34,924 participants). Characteristics of patients included in the 69 RCTs included in the networks are presented in Additional file 1. The impact of four patient characteristics on relative treatment effectiveness was investigated by producing four smaller networks: ‘no previous biologic use’ (<25% patients had prior exposure to a biologic therapy), ‘PASI  $\leq 25$ ’ (average PASI score was 25 or less), ‘weight  $\leq 90$  kg’ (average weight was 90 kg or less) and ‘white ethnicity’ ( $\geq 90\%$  patients were white). Cut-off choice was informed by clinical opinion as well as being pragmatically chosen in order to ensure a sufficient number of studies was still included in each network. The studies included in each of the four networks and the original (all licensed doses) network are listed in Table 2. The network diagrams are shown in Figures 1 to 5. The width of the connecting lines is proportional to the number of trial level comparisons available and the size of the nodes is proportional to the number of patients who received the corresponding treatment.

*Insert Table 2 here*

### ***Model fit***

In all models both a uniform (0,3) prior distribution and an empirically based log normal (-2.70,1.52<sup>2</sup>) informative prior distribution(15) were used. The random effects model with a uniform prior distribution was found to have a superior fit for the network of all studies with licensed doses (Table 3) as the residual deviance was closer to the number of unconstrained data points than the fixed effects model and the random effects model with log-normal prior distribution. The deviance information criterion (DIC) was also lower for the uniform prior random effects model than the other two models.

*Insert Table 3 here*

The random effects model with a log-normal prior distribution was chosen for the network of patients with no previous biologic use (<25% patients had previous biologic use), the network of patients with PASI score  $\leq 25$ , the network of patients with weight  $\leq 90$  kg and the network of  $\geq 90\%$  white patients (Table 3). The DIC and residual deviance was much lower for the random effects models than the fixed effects models. Although the DIC was very similar between the random effects models, the log-normal prior model was chosen as it had a much smaller number of parameters (pD) than the uniform prior model.

### ***Heterogeneity***

The network of all studies with licensed doses had the highest between-study heterogeneity (0.31, 95% CrI: 0.17-0.45). The between-study heterogeneity was reduced for the four smaller networks, which all had similar values. However, the network of patients with no previous biologic use had the smallest heterogeneity (0.14, 95% CrI: 0.09-0.23), alongside the network of patients with weight  $\leq 90$  kg (0.15, 95% CrI: 0.09-0.24). The densities of the posterior between-study heterogeneity for each network meta-analysis are shown in Figure 6.

### ***Effects of the interventions***

Relative risk ratios for each treatment compared against placebo are shown in Table 4. Across the five NMAs, the relative risks for each treatment appear to be similar, with all credible intervals overlapping. However, there are some noticeable differences. Etanercept 50 mg (once-weekly) had a higher relative treatment effect of achieving PASI 75 in the licensed doses network (10.67, 95% CrI: 7.96-13.53) compared to all other networks and methotrexate had a higher relative effect in the network of patients with no previous biologic use (<25% had previous use) (10.47, 95% CrI: 6.73-14.41) compared to the other networks. In the  $\geq 90\%$  white patients network, secukinumab had a higher relative treatment effect than in all other networks (18.67, 95% CrI: 16.22-20.81) and guselkumab had a lower relative treatment effect

1 compared to all the other networks (15.30, 95% CrI: 10.89-18.39). However, their credible  
2 intervals were large.

3 *Insert table 4 here*

4 Log-odds ratios for each network and for each treatment compared to placebo are shown in  
5 Figure 7. Absolute probabilities of achieving PASI 75 for each treatment across the five  
6 networks are shown in Additional file 2.

7 The median rankings of treatments based on the relative risks are shown in Table 5.

8 Ixekizumab ranks best in all networks, except the network with predominantly white patients,  
9 in which secukinumab ranks best. Dimethyl fumarate ranks worst in all five networks. The  
10 rankings are generally consistent across the networks. However, the NMA that included only  
11 studies in which less than 25% of patients had prior exposure to a biologic therapy had  
12 slightly different treatment rankings; the anti-TNF therapies certolizumab pegol (median rank  
13 of 8 [95% CrI: 2-13] for the 200mg dose and 6 [95% CrI: 1-11] for the 400 mg dose) and  
14 infliximab (median rank of 3 [95% CrI: 3-11]) ranked higher in this network group than any  
15 of the other networks, indicating that these two therapies may work better in patients who  
16 have not previously received biologic therapy, although we note the large uncertainty in these  
17 rankings. However, biologic experienced patients are more likely to have had prior exposure  
18 to an anti-TNF therapy (i.e. adalimumab or etanercept) which may explain why subsequent  
19 response to the anti-TNF therapies certolizumab pegol and infliximab was lower in the  
20 networks that did not include primarily biologic-naïve patients.

21 *Insert table 5 here*

22 The network of primarily white patients also had slightly different treatment rankings;  
23 secukinumab ranked higher and guselkumab ranked lower than in the other networks,

1 although there was large uncertainty for the guselkumab result. Data on ethnicity was often  
2 not reported in the included studies, so some assumptions had to be made based on the  
3 location of the study when extracting data from primary studies, adding further uncertainty to  
4 the results for this network.

### 5 *Sensitivity analysis*

6 Some studies of the earlier treatments for psoriasis, adalimumab, etanercept and infliximab,  
7 did not report prior biologic use, however they may have had largely biologic-naïve patient  
8 populations as biologics were not widely available at the time they were conducted.  
9 Therefore, all the studies not already included in the network of patients who had no prior  
10 biologic exposure (<25% patients) were screened and studies conducted prior to 2007, where  
11 prior biologic use was not reported, were added to the network. The cut-off of 2007 was  
12 chosen to ensure that all the earliest studies were included. Six studies conducted prior to  
13 2007 were identified and included in the network: Gottlieb et al. (2003),(16) Leonardi et al.  
14 (2003),(17) Papp et al. (2005),(18) Reich et al. (2005),(19) Gordon et al (2006)(20) and  
15 Tying et al. (2006).(21) The random effects model with a log-normal prior distribution was  
16 chosen for the network of patients with no previous biologic use (<25% patients had previous  
17 biologic use) (see Additional file 3, Table 1).

18 The results from the sensitivity analysis were very similar to the main results (see Additional  
19 file 3, Table 2). There were minimal changes to the risk ratios, with very little difference in  
20 the anti-TNF drugs adalimumab, infliximab and etanercept. There were a few small changes  
21 to other treatments. The median ranking of guselkumab changed from 3 to 4, with the same  
22 credible interval of 1-7. The median ranking of apremilast and DMF dropped one rank each,  
23 with the addition of etanercept 25 mg to the network, making the total number of treatments  
24 17, rather than 16.

## Discussion

The smaller networks investigated were less heterogeneous, with between-study standard deviation ranging from 0.14 (95% CrI: 0.09-0.23) for the network of patients with no previous biologic use to 0.17 (95% CrI: 0.10-0.25) for the network of predominantly white patients, in comparison with the network of all studies with licensed doses (0.31, 95% CrI: 0.17-0.45). The reduction in heterogeneity in the network of patients with no previous biologic use could be due to the population being more clinically homogenous. Previous biologic use may be an important effect modifier and so excluding patients with previous biologic use may have removed a significant source of heterogeneity.

Results for most of the NMAs were consistent, in terms of treatment rankings for PASI 75 response. The main exception was the NMA of studies in which  $\leq 25\%$  patients had prior exposure to a biologic therapy; in this network results were better for the anti-TNF therapies certolizumab pegol and infliximab than in the other networks. Whilst this could simply reflect the fact that studies in which a higher proportion of patients had prior exposure to a biologic therapy had used an anti-TNF as the prior therapy (i.e. adalimumab or etanercept), this may be an important effect modifier. Prior biologic therapy exposure was the most commonly conducted sensitivity analysis amongst the NICE STAs of systemic therapies for psoriasis that included a NMA (see Table 1) and our results confirm the importance of considering this as a potential effect modifier.

Meta-regression is another method commonly used to adjust for effect modifiers. However, this requires a sufficient number of studies in order to estimate independent coefficients for each treatment comparison. Additional file 4 presents the number of studies that reported each continuous covariate for each treatment comparison. This shows that there are not enough studies between comparisons to estimate independent coefficients and a common



1 regression coefficient would need to be assumed, which may not be clinically credible.  
2 Therefore, analyses were simplified by dichotomising variables according to clinically  
3 relevant cut-offs and creating separate networks. Previous work has investigated the effect of  
4 baseline risk using meta-regression.(22) Baseline risk is often a proxy for multiple observed  
5 and unobserved effect modifiers and does not describe specific individual patient-related  
6 treatment effect modifiers. Adjusting for baseline risk in this analysis may not be clinically  
7 meaningful for decision making since it is uncertain what determines the baseline risk. Our  
8 aim was to characterise heterogeneity based on known and previously hypothesised study-  
9 level characteristics that translate to individual patient characteristics, which can be used to  
10 focus decision-making on more specific, homogeneous populations.

11 A limitation of our analysis is the variation in time point at which PASI 75 was assessed in  
12 the included studies. In most included studies the time point for the primary efficacy  
13 assessment was week 12, although in some studies it was week 16; adalimumab, apremilast,  
14 certolizumab pegol, tildrakizumab and ustekinumab were assessed at week 12 in some  
15 studies and week 16 in others. The primary efficacy assessment was week 10 in placebo-  
16 controlled trials of infliximab, reflecting the shorter time to treatment effect for this therapy.

17 Our findings could be investigated further using individual patient data meta-analysis  
18 accounting for different important covariates. However, this preliminary approach has  
19 highlighted potential differences in treatment response for patients with prior exposure to  
20 biologic therapy. Where individual patient data are available, a better characterisation of  
21 patients' prior biologic use could be used to further explore the differences identified.

## 22 ***Comparison with other results***

23 Treatment rankings for the 'licenced doses' NMA were broadly consistent with the results of  
24 the NMA undertaken by the guideline development group for the BAD guidelines for

biologic therapy for psoriasis, published in April 2017.(23) The BAD NMA compared ixekizumab, secukinumab, infliximab, ustekinumab, adalimumab, etanercept, methotrexate and placebo. Interventions were ranked in order of efficacy using the surface under the cumulative ranking (SUCRA) curve method. For the outcome PASI 75 at 3-4 months ixekizumab ranked best (SUCRA 96.4, mean rank 1.3), followed by infliximab (SUCRA 81.2, mean rank 2.3), secukinumab (SUCRA 79.0, mean rank 2.5), ustekinumab (SUCRA 51.9, mean rank 4.4), adalimumab (SUCRA 48.7, mean rank 4.6), etanercept (SUCRA 28.4, mean rank 6.0), methotrexate (SUCRA 14.5, mean rank 7.0) and placebo (SUCRA 0, mean rank 8.0). However, the BAD NMA pooled licensed and unlicensed doses.(24) It included many unlicensed doses that were not included in this analysis as they are not relevant for decision-making. Naïve pooling across doses, without accounting for possible differential dose effects, is not recommended as it can increase heterogeneity due to different treatment definitions. Furthermore, the aim of this analysis was to characterise heterogeneity in networks used by NICE, therefore only licenced doses were relevant.

A recent article evaluated the association between patient characteristics and response to biologic therapies for psoriasis, using a multicentre longitudinal cohort study; the British Association of Dermatologists Biologic Interventions Register (BADBIR).(25) This study also found little evidence for predictors of differential treatment response, although only biologic-naïve patients were included in the study.

## ***Network structure***

There was some overlap between networks in terms of included studies (see Table 2). In particular many of the studies excluded from the  $\geq 90\%$  white patients network were included in the network of studies with lighter patients ( $\leq 90$  kg). Only ten studies included patients

with a mean weight below 80 kg, nine of which were conducted in Japanese, Chinese or mixed Taiwanese, Chinese and Korean patients (See Additional file 1).

### ***Recommendations for future research***

NMAs of psoriasis treatments undertaken in the future should investigate heterogeneity within the networks and include clinically relevant subgroups to further investigate effect modification related to certain patient characteristics. This recommendation is also appropriate for NMAs in other clinical areas and other fields outside of medicine.

### **Conclusions**

This work has highlighted potential differences in relative treatment effectiveness for biologic-naïve patients receiving psoriasis treatment. Our results support the assumption that prior exposure to biologic therapy is associated with psoriasis treatment response and confirm the importance of considering this as a potential effect modifier. Future decision-making on psoriasis treatments should consider patients' prior exposure to biologic therapies. ~~this subgroup when undertaking network meta-analysis.~~

More broadly, we have demonstrated the importance of assessing heterogeneity in patient characteristics and adjusting for effect modifiers in a NMA, which can be done by restricting inclusion in the NMA to certain subgroups of patients with similar characteristics. Focusing the inclusion criteria to produce smaller, more homogenous networks can reduce the risk of both heterogeneity and inconsistency, and give more valid results.

### **List of abbreviations**

|        |   |
|--------|---|
| BADBIR | British Association of Dermatologists Biologic Interventions Register |
| DLQI   | Dermatology Life Quality Index  |
| DIC    | Deviance information criterion  |
| IL     | Interleukin   |

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| 1 | NICE  | National Institute for Health and Care Excellence |
| 2 | NMA   | Network meta-analysis                             |
| 3 | Nrf2  | Nuclear factor (erythroid-derived 2)-like 2       |
| 4 | PDE   | Phosphodiesterase                                 |
| 5 | PASI  | Psoriasis Area and Severity Index                 |
| 6 | RCT   | Randomised controlled trial                       |
| 7 | STA   | Single Technology Appraisal                       |
| 8 | SUCRA | Surface under the cumulative ranking              |
| 9 | TNF   | Tumour necrosis factor                            |

**Declarations**

*Ethics approval and consent to participate*

Not applicable.

*Consent for publication*

Not applicable.

*Availability of data and materials*

All data generated or analysed during this study are included in this published article (and its supplementary information files).

*Competing interests*

The authors declare that they have no competing interests.

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***Authors' contributions***

RW conceived and designed the project. RW and SS identified the relevant NMAs and primary studies and tabulated important study and patient characteristics. SS undertook network meta-analyses under the supervision of SD. All authors contributed to drafting the manuscript and approved the submitted version.

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RW has almost 20 years' experience of undertaking systematic reviews. She has completed three NICE STAs of systemic therapies for the second-line treatment of moderate-to-severe plaque psoriasis. SS is a systematic reviewer with experience in medical statistics who has also been involved in a NICE STA of a systemic therapy for psoriasis. SD is a statistician with interests in Bayesian methods for evidence synthesis and their application to decision making. She has collaborated with the NICE Decision Support Unit to produce several technical support documents which provide guidance to those involved in submitting or critiquing evidence as part of NICE Technology Appraisals and is lead author of a recent book on network meta-analysis for decision making.

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1 **Table 2: Studies included in each network meta-analysis**

| Studies          | All<br>licensed<br>doses<br>(N=69) | Patients<br>with no<br>previous<br>biologic use<br>( $<25\%$ had<br>previous<br>use)<br>(N=34) | Patients<br>with PASI<br>score $\leq 25$<br>(N=59) | Patients<br>with weight<br>$\leq 90$ kg<br>(N=28) | White<br>patients<br>( $\geq 90\%$<br>white)<br>(N=42) |
|------------------|------------------------------------|--|--|---|--|
| AMAGINE1 2016    | ✓                                  |  | ✓  |   | ✓  |
| AMAGINE2 2015    | ✓                                  |  | ✓  |   | ✓  |
| AMAGINE3 2015    | ✓                                  | ✓  | ✓  | ✓   | ✓  |
| Nakagawa 2016    | ✓                                  | ✓  |  | ✓   |  |
| Papp 2012        | ✓                                  |  | ✓  | ✓   |  |
| CHAMPION 2008    | ✓                                  |  | ✓  | ✓   | ✓  |
| Goldminz 2015    | ✓                                  |  | ✓  |   |  |
| Cai 2016         | ✓                                  | ✓  |  | ✓   |  |
| REVEAL 2008      | ✓                                  | ✓  | ✓  |   | ✓  |
| Asahina 2010     | ✓                                  |  |  | ✓   |  |
| Gordon 2006      | ✓                                  |  | ✓  |   | ✓  |
| XPLORE 2015      | ✓                                  |  | ✓  |   | ✓  |
| Bissonnette 2013 | ✓                                  |  | ✓  |   | ✓  |
| VOYAGE1 2017     | ✓                                  | ✓  | ✓  |   |  |
| VOYAGE2 2017     | ✓                                  | ✓  | ✓  |   |  |
| PSOR005 2012     | ✓                                  |  | ✓  |   | ✓  |
| ESTEEM1 2015     | ✓                                  |  | ✓  |   | ✓  |

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|-------------------|---|---|---|---|---|
| ESTEEM2 2015      | ✓ |   | ✓ |   | ✓ |
| Ohtsuki 2017      | ✓ | ✓ | ✓ | ✓ |   |
| LIBERATE 2016     | ✓ | ✓ | ✓ | ✓ | ✓ |
| Leonardi 2003     | ✓ |   | ✓ |   |   |
| Gottlieb 2003     | ✓ |   | ✓ |   | ✓ |
| Papp 2005         | ✓ |   | ✓ |   | ✓ |
| VandeKerkhof 2008 | ✓ |   | ✓ | ✓ | ✓ |
| Bagel 2012        | ✓ | ✓ | ✓ |   |   |
| Bachelez 2015     | ✓ | ✓ | ✓ | ✓ |   |
| Tyring 2006       | ✓ |   | ✓ |   |   |
| PRISTINE 2013     | ✓ | ✓ | ✓ | ✓ |   |
| M10114 2011       | ✓ | ✓ | ✓ |   | ✓ |
| M10315 2011       | ✓ | ✓ | ✓ |   | ✓ |
| reSURFACE2        | ✓ | ✓ | ✓ | ✓ | ✓ |
| PIECE 2016        | ✓ | ✓ | ✓ |   | ✓ |
| Yang 2012         | ✓ |   | ✓ | ✓ |   |
| EXPRESS 2005      | ✓ |   | ✓ | ✓ |   |
| Chaudhari 2001    | ✓ | ✓ | ✓ | ✓ | ✓ |
| SPIRIT 2004       | ✓ |   | ✓ |   | ✓ |
| EXPRESSII 2007    | ✓ | ✓ | ✓ |   | ✓ |
| Torii 2010        | ✓ |   |   | ✓ |   |
| RESTORE1 2011     | ✓ | ✓ | ✓ | ✓ | ✓ |
| UNCOVER1 2016     | ✓ |   | ✓ |   | ✓ |
| UNCOVER2 2015     | ✓ | ✓ | ✓ |   | ✓ |
| UNCOVER3 2015     | ✓ | ✓ | ✓ |   | ✓ |
| IXORAS 2017       | ✓ | ✓ | ✓ | ✓ | ✓ |
| FEATURE 2015      | ✓ |   | ✓ |   | ✓ |

|               |   |   |   |   |   |
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| ERASURE 2014  | ✓ |   | ✓ | ✓ |   |
| FIXTURE 2014  | ✓ | ✓ | ✓ | ✓ |   |
| JUNCTURE 2015 | ✓ | ✓ | ✓ |   | ✓ |
| CLEAR 2015    | ✓ | ✓ | ✓ | ✓ |   |
| PEARL 2011    | ✓ | ✓ | ✓ | ✓ |   |
| PHOENIX1 2008 | ✓ |   | ✓ |   | ✓ |
| PHOENIX2 2008 | ✓ |   | ✓ |   | ✓ |
| LOTUS 2013    | ✓ | ✓ | ✓ | ✓ |   |
| ACCEPT 2010   | ✓ | ✓ | ✓ |   | ✓ |
| Igarashi 2012 | ✓ | ✓ |   | ✓ |   |
| BRIDGE 2017   | ✓ | ✓ | ✓ |   | ✓ |
| Caproni 2009  | ✓ |   | ✓ |   | ✓ |
| Gisondi 2008  | ✓ |   | ✓ |   | ✓ |
| Meffert       | ✓ |   |   |   | ✓ |
| PappD 2015    | ✓ | ✓ |   |   |   |
| ReSURFACE1    | ✓ | ✓ | ✓ | ✓ |   |
| ultIMMA1      | ✓ |   |   |   |   |
| ultIMMA2      | ✓ |   |   |   |   |
| METOP         | ✓ | ✓ | ✓ |   | ✓ |
| Krueger       | ✓ |   | ✓ |   |   |
| Reich 2012    | ✓ | ✓ | ✓ | ✓ | ✓ |
| CIMPACT 2018  | ✓ |   | ✓ | ✓ | ✓ |
| CIMPASI1 2018 | ✓ |   | ✓ |   | ✓ |
| CIMPASI2 2018 | ✓ |   | ✓ |   | ✓ |
| UNVEIL        | ✓ | ✓ | ✓ | ✓ | ✓ |

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**Table 3: Measures of goodness of fit of fixed and random effects models for each of the five network meta-analyses.**

| Measure of goodness of fit  | Random effects<br>(uniform prior) | Random effects<br>(log-normal<br>prior) | Fixed effects |
|---|-----------------------------------|---|---------------|
| <b>Licensed doses network</b>   |                                   |   |               |
| Residual deviance <sup>1</sup>  | 162.78                            | 177.54                                  | 209.77        |
| pD  | 117.98                            | 106.29                                  | 91.61         |
| Deviance information criterion<br>(DIC)   | 280.76                            | 283.83                                  | 301.38        |
| Between-study standard deviation,<br>posterior median (95% credible<br>interval)    | 0.31 (0.17-0.45)                  | 0.19 (0.12-0.28)                        | -             |
| <b>Network of patients with no previous biologic use (&lt;25% had previous use)</b> |                                   |   |               |
| Residual deviance <sup>2</sup>  | 82.10                             | 82.88                                   | 88.85         |
| pD  | 59.12                             | 56.3                                    | 52.45         |
| Deviance information criterion<br>(DIC)   | 141.22                            | 139.20                                  | 141.30        |
| Between-study standard<br>deviation, posterior median (95%<br>credible interval)    | 0.19 (0.01-0.41)                  | 0.14 (0.09-0.23)                        | -             |
| <b>Network of patients with PASI score ≤25</b>                                      |                                   |   |               |
| Residual deviance <sup>3</sup>  | 143.89                            | 152.67                                  | 173.06        |
| pD  | 99.16                             | 90.58                                   | 79.61         |
| Deviance information criterion<br>(DIC)   | 243.05                            | 243.26                                  | 252.67        |

|  |                      |                  |        |
|--|----------------------|------------------|--------|
| Between-study standard deviation, posterior median (95% credible interval) | 0.2574 (0.114-0.408) | 0.16 (0.10-0.24) | -      |
| <b>Network of patients with weight <math>\leq 90</math> kg</b>             |                      |                  |        |
| Residual deviance <sup>4</sup>   | 66.40                | 74.17            | 80.02  |
| pD   | 51.59                | 44.78            | 42.14  |
| Deviance information criterion (DIC)                                       | 117.99               | 118.95           | 122.16 |
| Between-study standard deviation, posterior median (95% credible interval) | 0.40 (0.08-0.76)     | 0.15 (0.09-0.24) | -      |
| <b>Network of <math>\geq 90\%</math> white patients</b>                    |                      |                  |        |
| Residual deviance <sup>5</sup>   | 100.57               | 112.47           | 126.65 |
| pD   | 78.57                | 71.62            | 63.83  |
| Deviance information criterion (DIC)                                       | 179.14               | 184.09           | 190.48 |
| Between-study standard deviation, posterior median (95% credible interval) | 0.311 (0.13-0.51)    | 0.17 (0.10-0.25) | -      |

<sup>1</sup>165 unconstrained data points, pD number of parameters for Licensed doses network <sup>2</sup>80 unconstrained data points, pD

number of parameters <sup>3</sup>143 unconstrained data points, pD number of parameters <sup>4</sup>65 unconstrained data points,

pD number of parameters <sup>5</sup>103 unconstrained data points, pD number of parameters

- 1     ***Table 4: Median risk ratio for each treatment compared against placebo in all five network***
- 2     ***meta-analyses***

| Treatment                          | Median risk ratio versus placebo – PASI 75<br>(95% CrI) |                                    |                        |                        |                        |
|------------------------------------|---|------------------------------------|------------------------|------------------------|------------------------|
|                                    | All licensed<br>doses                                   | No previous<br>biologic use (<25%) | PASI score<br>≤25      | Weight ≤90<br>kg       | ≥90% white<br>patients |
| Adalimumab 40 mg                   | 12.74<br>(11.00-14.49)                                  | 12.48<br>(10.91-14.13)             | 13.09<br>(11.72-14.57) | 12.87<br>(10.29-15.39) | 13.18<br>(11.21-15.15) |
| Brodalumab 210 mg                  | 16.76<br>(15.12-18.53)                                  | 16.45<br>(14.66-18.31)             | 16.62<br>(15.20-18.18) | 16.73<br>(14.97-18.58) | 16.56<br>(15.02-18.24) |
| Certolizumab 200 mg                | 12.07<br>(9.62-14.54)                                   | 13.93<br>(8.63-18.20)              | 12.08<br>(10.30-13.94) | 11.71<br>(9.11-14.27)  | 12.13<br>(10.02-14.26) |
| Certolizumab 400 mg                | 13.47<br>(11.09-15.80)                                  | 15.73<br>(10.81-19.08)             | 13.42<br>(11.65-15.23) | 13.04<br>(10.53-15.46) | 13.48<br>(11.42-15.52) |
| Etanercept 25 mg                   | 7.61<br>(5.52-10.11)                                    | -                                  | 7.64<br>(6.20-9.20)    | -                      | 7.89<br>(5.60-10.51)   |
| Etanercept 50 mg<br>once-weekly    | 10.67<br>(7.96-13.53)                                   | 5.08<br>(3.50-7.07)                | 6.16<br>(4.69-7.90)    | 5.57<br>(3.91-7.65)    | 7.07<br>(4.57-10.20)   |
| Etanercept 50 mg<br>twice per week | 9.90<br>(8.68-11.21)                                    | 9.46<br>(8.27-10.77)               | 10.40<br>(9.47-11.40)  | 9.85<br>(8.27-11.55)   | 10.33<br>(9.01-11.75)  |
| Guselkumab 100 mg                  | 17.06<br>(15.30-18.91)                                  | 16.68<br>(15.07-18.42)             | 16.83<br>(15.32-18.46) | -                      | 15.30<br>(10.89-18.39) |
| Infliximab 5 mg                    | 16.22<br>(14.37-18.15)                                  | 16.88<br>(14.66-19.03)             | 15.46<br>(13.85-17.17) | 14.19<br>(11.76-16.56) | 15.38<br>(13.41-17.36) |
| Ixekizumab 80mg                    | 17.64<br>(16.06-19.36)                                  | 17.42<br>(15.89-19.09)             | 17.79<br>(16.30-19.41) | 17.16<br>(14.67-19.33) | 17.75<br>(16.23-19.41) |
| Risankizumab 150 mg                | 16.46<br>(14.37-18.47)                                  | -                                  | -                      | -                      | -                      |

|                                 |                        |                        |                        |                        |                        |
|---------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| Secukinumab 300 mg              | 16.45<br>(14.79-18.23) | 16.03<br>(14.41-17.73) | 16.43<br>(15.03-17.96) | 16.12<br>(14.55-17.82) | 18.67<br>(16.22-20.81) |
| Ustekinumab 45 mg               | 13.59<br>(11.79-15.44) | 12.20<br>(10.32-14.14) | 13.46<br>(12.17-14.84) | 13.04<br>(10.35-15.63) | 13.68<br>(11.95-15.48) |
| Ustekinumab 90 mg               | 14.67<br>(12.85-16.54) | 13.36<br>(11.29-15.38) | 14.51<br>(13.20-15.95) | 14.36<br>(10.18-17.57) | 14.64<br>(13.00-16.37) |
| Ustekinumab (45 mg<br>or 90 mg) | 12.85<br>(11.07-14.67) | 12.96<br>(11.05-14.94) | 13.19<br>(11.79-14.66) | 13.11<br>(10.99-15.20) | 13.14<br>(11.35-14.95) |
| Tildrakizumab 100 mg            | 14.86<br>(12.49-17.02) | 15.03<br>(13.18-16.91) | 15.82<br>(14.25-17.50) | 15.28<br>(13.31-17.21) | 16.21<br>(14.20-18.16) |
| Apremilast                      | 5.80<br>(4.20-7.61)    | 3.77<br>(2.48-5.59)    | 5.17<br>(4.01-6.61)    | 3.91<br>(2.60-5.79)    | 5.46<br>(4.12-7.10)    |
| Dimethyl Fumarate               | 2.97<br>(1.44-5.73)    | 2.97<br>(1.77-4.88)    | 2.97<br>(1.71-5.01)    | -                      | 2.96<br>(1.71-4.98)    |
| Fumaderm                        | 3.31<br>(1.62-6.26)    | 3.32<br>(1.97-5.41)    | 3.31<br>(1.94-5.53)    | -                      | 3.30<br>(1.92-5.48)    |
| Methotrexate                    | 6.15<br>(4.07-8.65)    | 10.47<br>(6.73-14.41)  | 6.50<br>(4.69-8.60)    | 5.49<br>(3.56-8.12)    | 6.30<br>(4.37-8.61)    |
| Acitretin                       | 4.024<br>(1.55-8.39)   | -                      | 4.07<br>(1.59-8.29)    | -                      | 4.29<br>(1.74-8.43)    |
| Cyclosporin 1.5 mg              | 8.10<br>(2.41-16.91)   | -                      | -                      | -                      | 2.14<br>(0.38-10.53)   |
| Cyclosporin 2.5 mg              | 7.10<br>(2.02-16.34)   | -                      | -                      | -                      | 6.76<br>(2.07-16.03)   |

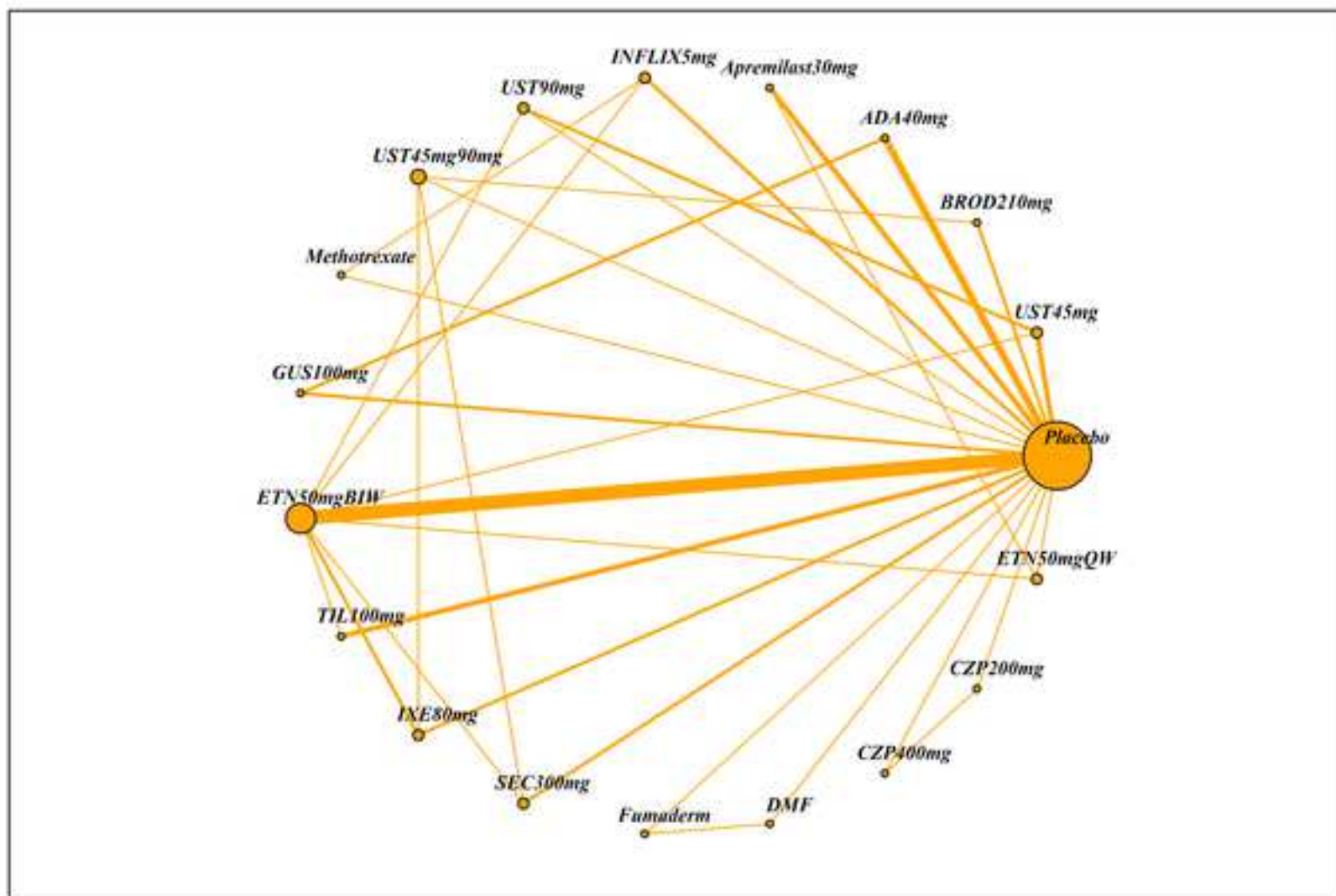


**Table 5: Median rank of treatments according to PASI 75 response in each of the five networks**

| Treatment                                   | Median rank (95% CrI)     |   |                           |                          |                                |
|---|---------------------------|---|---------------------------|--------------------------|--------------------------------|
|   | Licensed<br>Doses<br>N=69 | No previous<br>biologic use<br>(<25%)<br>N=34 | PASI score<br>≤25<br>N=59 | Weight<br>≤90 kg<br>N=27 | ≥90% white<br>patients<br>N=42 |
| <b>Adalimumab</b>                           | 11 (8-14)                 | 11 (8-12)                                     | 10 (7-12)                 | 9 (5-11)                 | 10 (7-12)                      |
| <b>Apremilast</b>                           | 17 (16-18)                | 15 (14-16)                                    | 16 (15-16)                | 14 (13-14)               | 16 (15-16)                     |
| <b>Brodalumab</b>                           | 3 (1-6)                   | 4 (1-7)                                       | 3 (2-5)                   | 2 (1-4)                  | 4 (2-6)                        |
| <b>Certolizumab 200 mg</b>                  | 13 (9-15)                 | 8 (2-13)                                      | 12 (9-12)                 | 11 (7-12)                | 12 (8-13)                      |
| <b>Certolizumab 400 mg</b>                  | 10 (7-13)                 | 6 (1-11)                                      | 9 (7-11)                  | 8 (5-11)                 | 9 (6-11)                       |
| <b>DMF</b>                                  | 18 (17-18)                | 16 (14-16)                                    | 17 (17-17)                | -                        | 17 (17-17)                     |
| <b>Etanercept 25mg</b>                      | 16 (15-17)                | -   | 14 (14-15)                | -                        | 14 (13-16)                     |
| <b>Etanercept 50mg<br/>(twice per week)</b> | 15 (14-15)                | 13 (12-13)                                    | 13 (13-13)                | 12 (11-12)               | 13 (12-14)                     |

|  |            |            |            |            |            |
|--|------------|------------|------------|------------|------------|
| <b>Etanercept 50mg<br/>(once-weekly)</b> | 14 (10-16) | 14 (14-15) | 15 (14-16) | 13 (13-14) | 15 (13-16) |
| <b>Guselkumab</b>                        | 2 (1-6)    | 3 (1-7)    | 2 (2-5)    | -          | 6 (2-12)   |
| <b>Infliximab</b>                        | 5 (2-8)    | 3 (1-7)    | 6 (3-7)    | 6 (3-10)   | 5 (3-9)    |
| <b>Ixekizumab</b>                        | 1 (1-4)    | 1 (1-4)    | 1 (1-1)    | 1 (1-5)    | 2 (1-3)    |
| <b>Risankizumab</b>                      | 4 (1-8)    | -          | -          | -          | -          |
| <b>Secukinumab</b>                       | 4 (2-7)    | 5 (2-7)    | 4 (2-6)    | 3 (1-5)    | 1 (1-3)    |
| <b>Tildrakizumab</b>                     | 7 (4-12)   | 7 (4-9)    | 5 (3-7)    | 4 (2-7)    | 4 (3-7)    |
| <b>Ustekinumab 45 mg</b>                 | 10 (8-13)  | 11 (8-12)  | 9 (8-12)   | 8 (5-11)   | 9 (6-12)   |
| <b>Ustekinumab 45<br/>mg/90 mg</b>       | 11 (8-14)  | 10 (7-12)  | 10 (7-12)  | 8 (5-11)   | 10 (6-12)  |
| <b>Ustekinumab 90 mg</b>                 | 8 (5-10)   | 9 (7-12)   | 7 (6-8)    | 6 (1-11)   | 7 (5-9)    |
| <b>Total number of<br/>treatments</b>    | 18         | 16         | 17         | 14         | 17         |

**Figure 2 Network of studies of patients with no previous biologic exposure (<25%)**



**Figure 1 Network of all studies with licensed treatment doses**

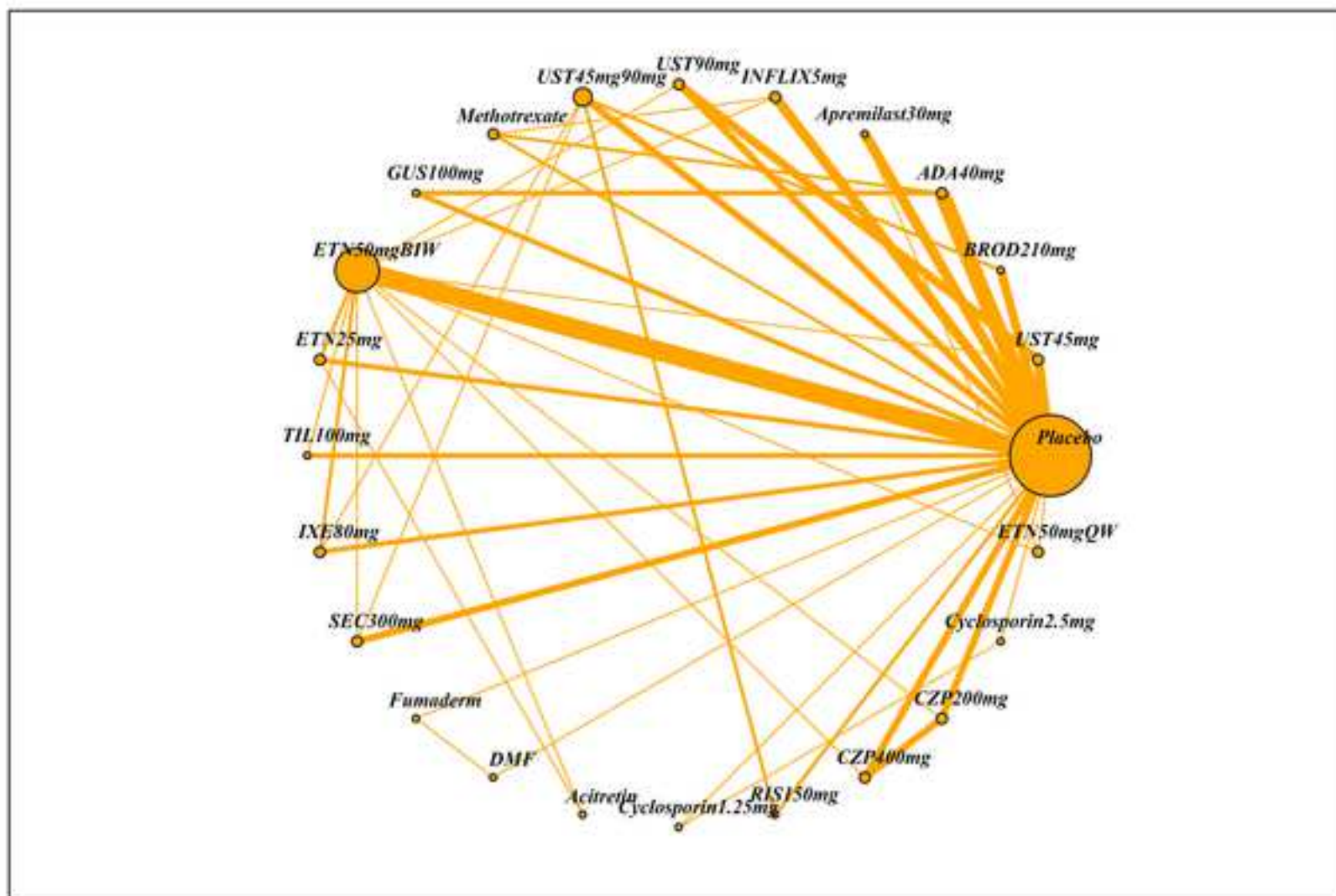


Figure 3 Network of studies of patients with PASI  $\leq 25$

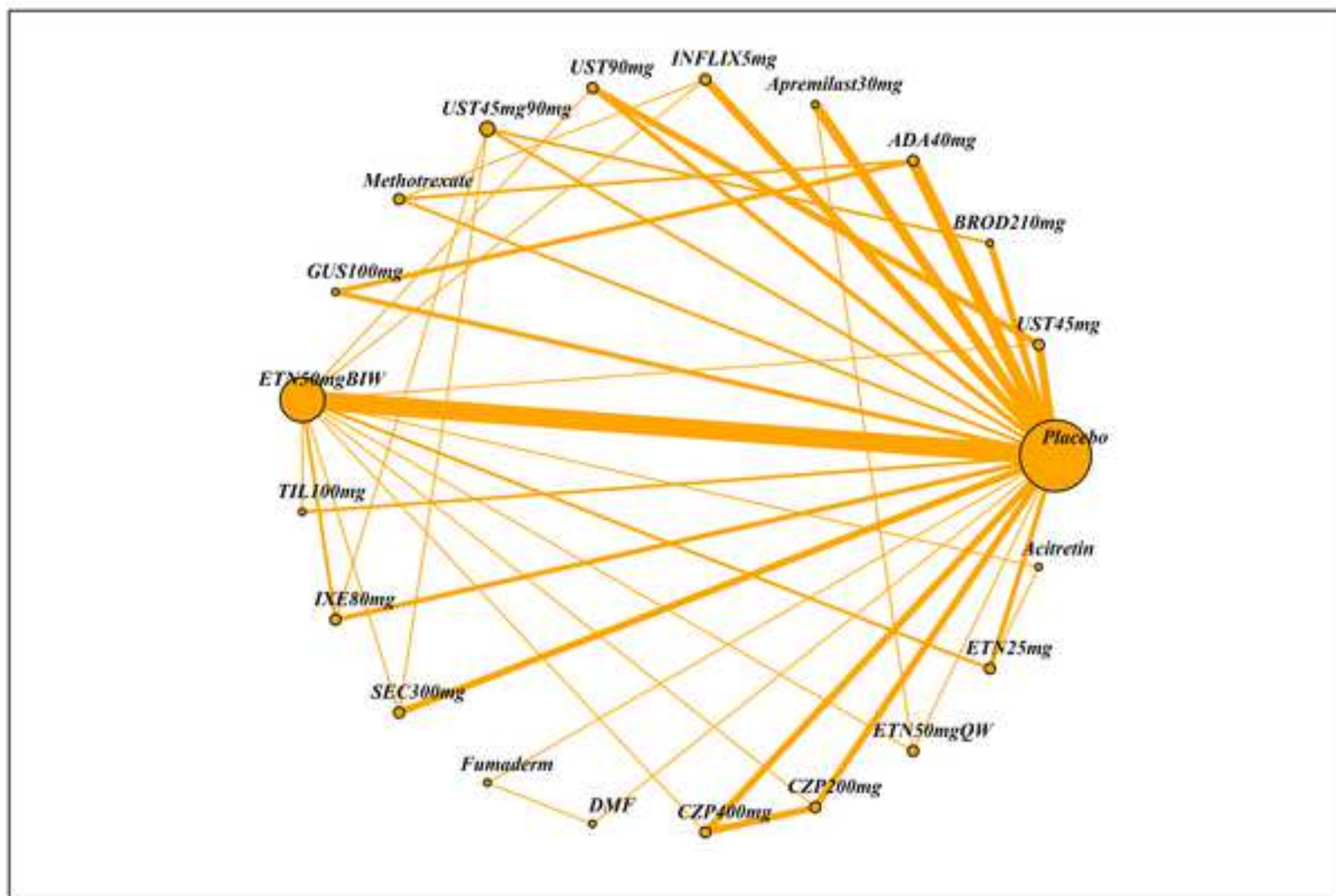
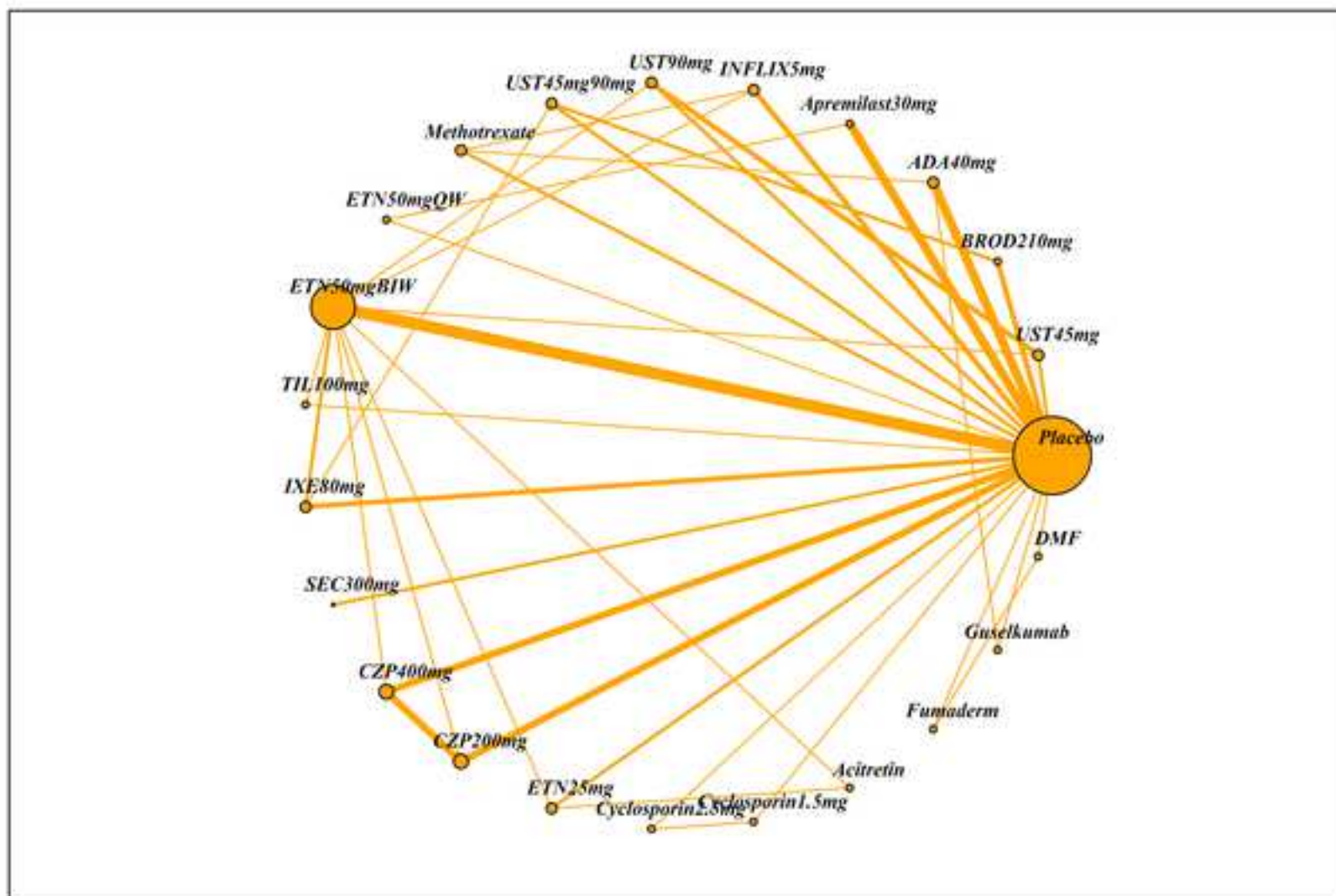


Figure 4 Network of studies of patients with weight  $\leq 90$  kg





**Figure 5 Network of studies including >90% white patients**

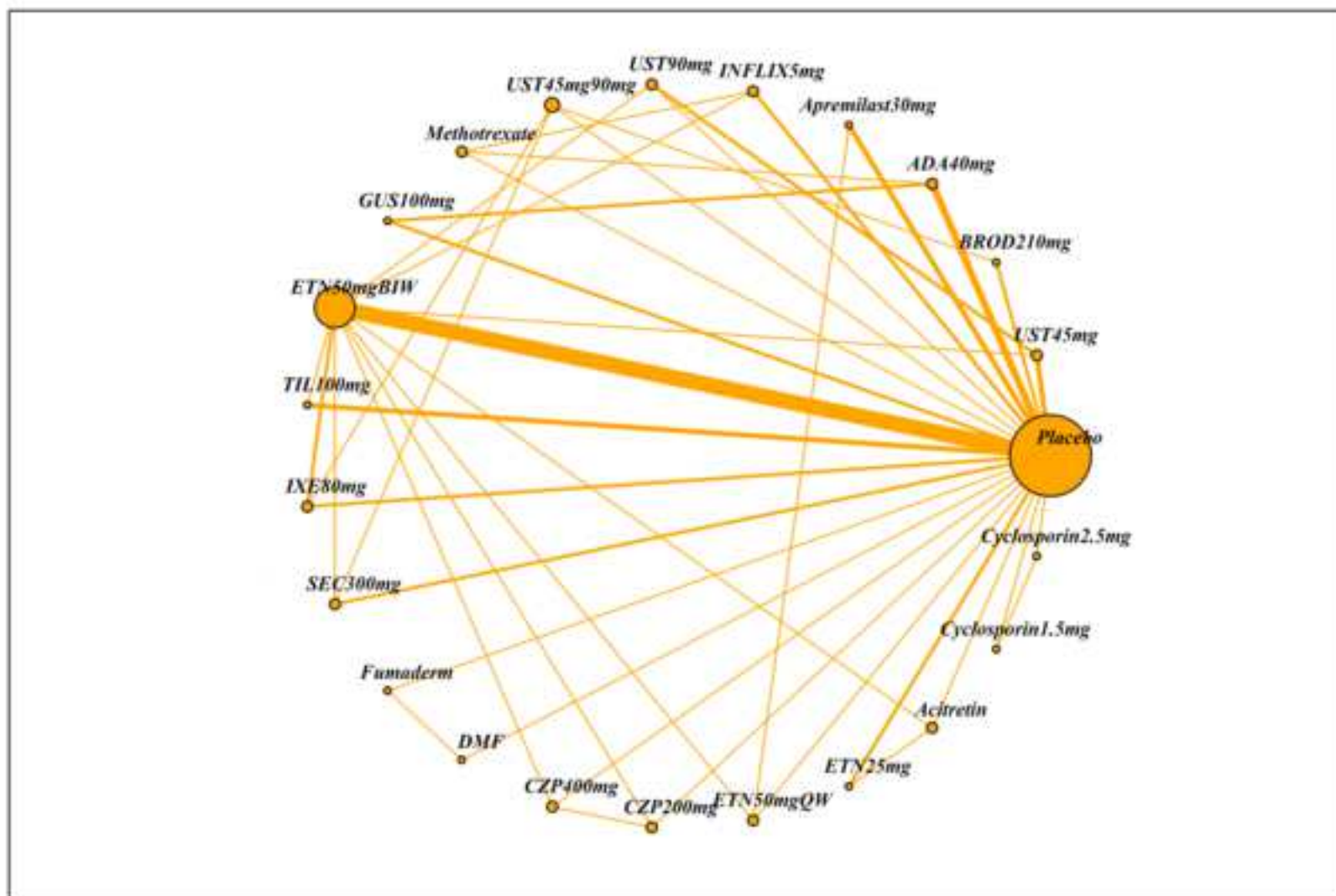
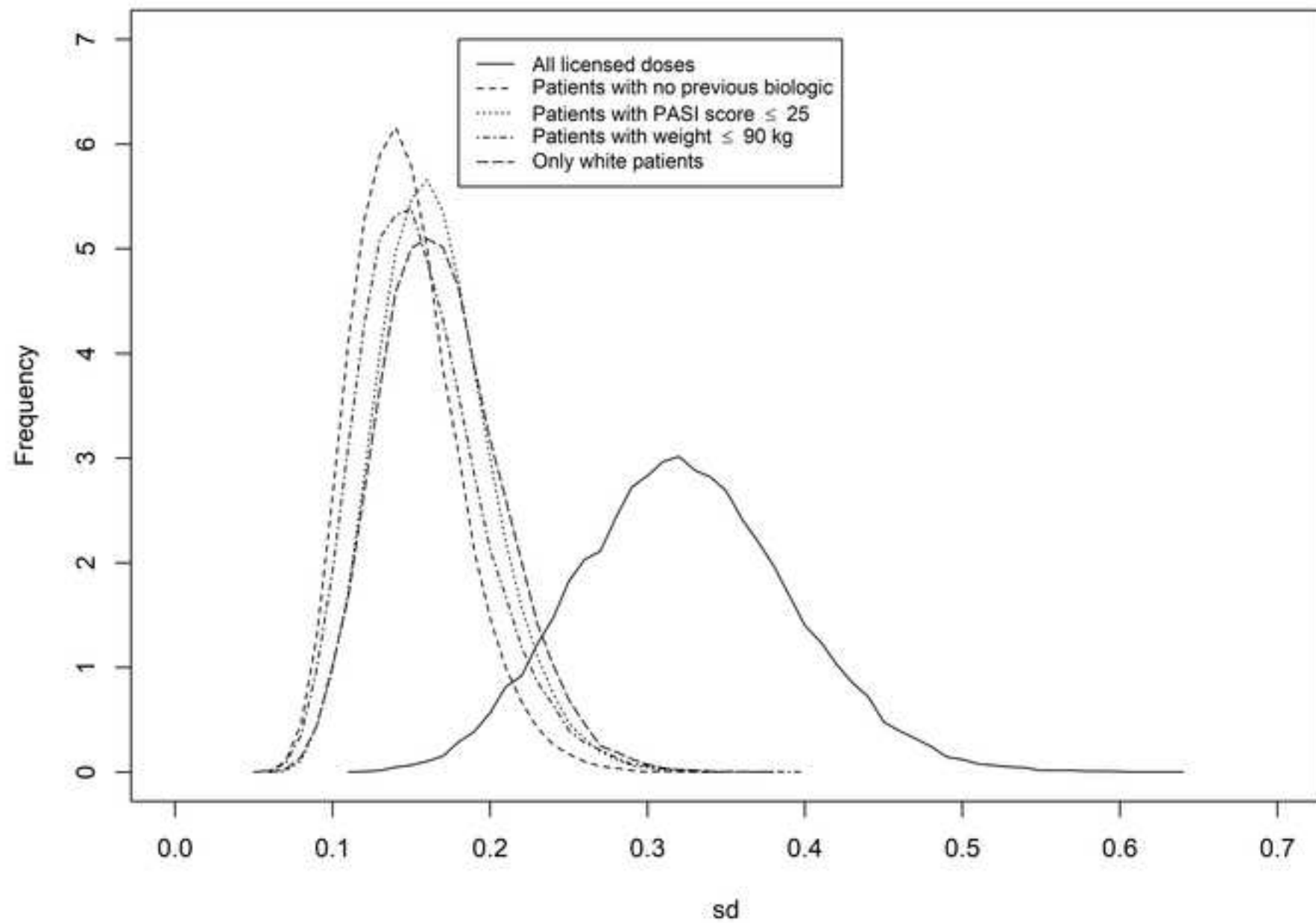
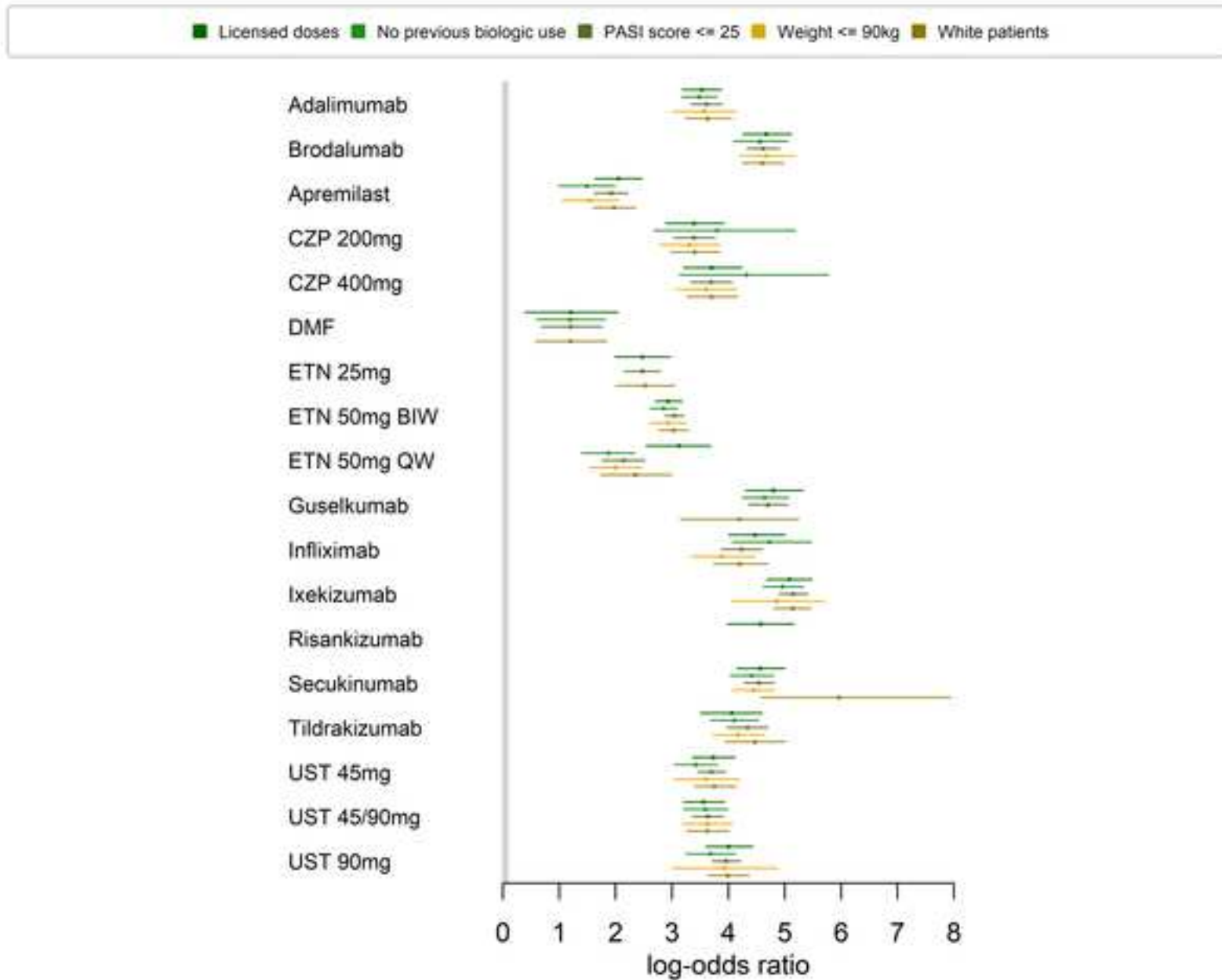


Figure 6 Posterior between-study heterogeneity density for the five NMAs





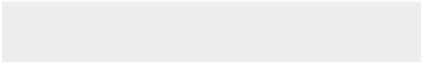

**Figure 7 Relative treatment effects split by network group for each treatment**



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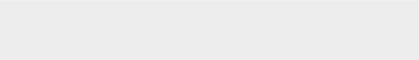





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